AMERICAN ACADEMY
OF OPHTHALMOLOGY®

EyeNet®

JANUARY 2019

Virtual Reality
Transforming Education

New Gains Against Fungal Keratitis
Diagnostic Tools, Cross-Linking

3 Experts Discuss Target IOP

EHR Users: Turn to Page 51 for New MIPS Rules at a Glance

INDICATION[1]

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

- Worsening or new onset congestive heart failure (CHF) may occur; exercise caution and monitor carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc.

Please see Brief Summary of full Prescribing Information on the following pages.

HUMIRA®
adalimumab
destination you™

F1RST AND ONLY FDA-APPROVED ANTI-TNF FOR TREATING NON-INFECTIOUS (NI) UVEITIS*

For adult patients with non-infectious (NI) intermediate, posterior, and panuveitis[1]

NON-INFECTIOUS (NI) UVEITIS* CAN BE HARD TO CONTROL.

HUMIRA is proven to[1]:

- Provide steroid-sparing efficacy
- Prolong time to a combined measure of disease flare† and decrease of visual acuity

Visit www.HumiraPro.com/uveitis to learn more.

*Intermediate, posterior, and panuveitis.

†Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal and/or retinal vascular lesions.

abbvie

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) plaque psoriasis (Ps), hidradenitis suppurativa (HS), and uveitis (UV) malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

Clinical Trials Experience

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
Adverse Reaction (Preferred Term)	(N=705)	(N=690)
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions and Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other

week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [*see Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**

  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**

  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**

  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**

  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

AbbVie Inc.
North Chicago, IL 60064, U.S.A.
US License Number 1889

Ref: 03-B374 Revised July 2016

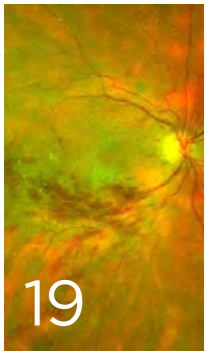
64C-1865519 **MASTER**

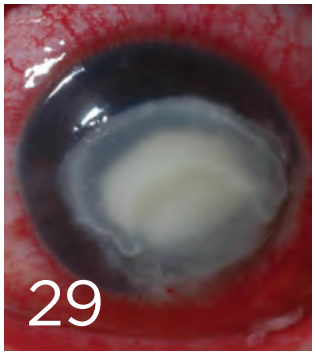
64C-1875312

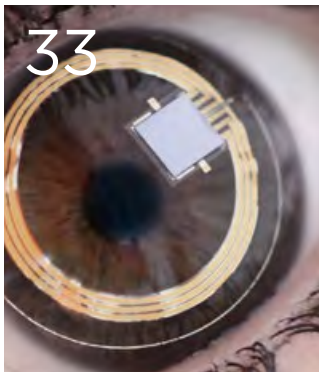
abbvie

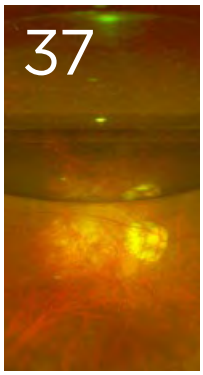
CONTENTS

JANUARY 2019
VOLUME 23 • NUMBER 1



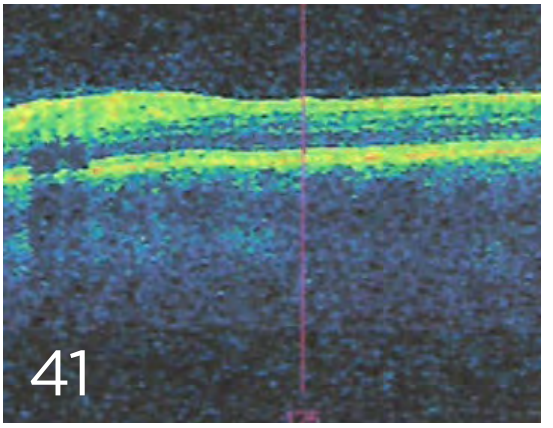


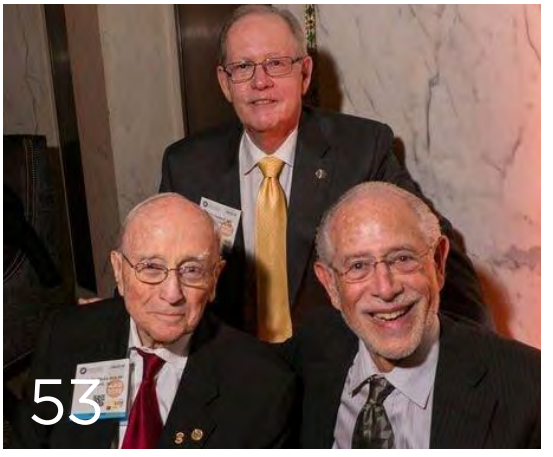


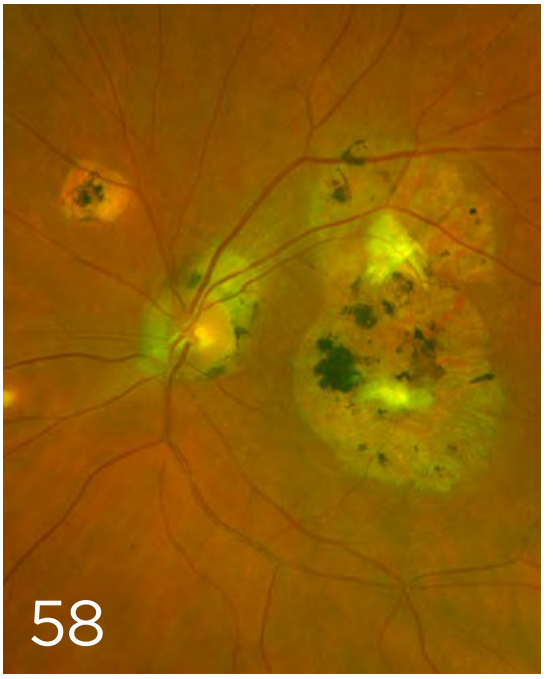


AMERICAN ACADEMY OF OPHTHALMOLOGY®

***EyeNet*® Magazine** (ISSN 1097-2986) is published monthly by the American Academy of Ophthalmology, 655 Beach St., San Francisco, CA 94109-1336, as a membership service. Subscription is included in U.S. members' annual dues. International Member, IMIT, $135 per year. Nonmember in U.S., $150 per year. Nonmember outside U.S., $210 per year. Periodicals Postage Paid at San Francisco, CA, and at additional mailing offices. POSTMASTER: Send address changes to *EyeNet*, P.O. Box 7424, San Francisco, CA 94120-7424.







WillsEye Hospital

Believing is Seeing

Wills Eye Hospital brings together leaders of every subspecialty in ophthalmology. It's a special place where "Skill with Compassion" is not just our motto, it's at our very core, our guiding principle.

840 Walnut St., Philadelphia, PA 19107 | willseye.org | 877.289.4557

EDITORIAL BOARD

ACADEMY BOARD

Learn more about the Board *at aao.org/bot.*

EyeNet® MAGAZINE

David W. Parke II, MD
Editor-in-Chief

Ruth D. Williams, MD
Chief Medical Editor

Dale E. Fajardo, EdD, MBA
Publisher

Patty Ames
Executive Editor

Carey S. Ballard
Art Director / Production Manager

Chris McDonagh, Jean Shaw
Senior Editors

Krista Thomas
Assistant Editor / Advertising Manager

Lori Baker-Schena, MBA, EdD; Leslie Burling; Peggy Denny; Miriam Karmel; Mike Mott; Linda Roach; Lynda Seminara; Annie Stuart; Gabrielle Weiner
Contributing Writers

Mark Mrvica, Kelly Miller
M.J. Mrvica Associates, Inc.
2 West Taunton Ave.,
Berlin, NJ 08009
856-768-9360
mjmrvica@mrvica.com
Advertising Sales

AMERICAN ACADEMY OF OPHTHALMOLOGY®
655 Beach St.
San Francisco, CA 94109
866-561-8558, 415-561-8500
aao.org

Governmental Affairs Division
20 F Street NW, Suite 400
Washington, DC 20001
202-737-6662

ARTICLE REVIEW PROCESS. Articles involving single-source medical and technical news are sent to quoted sources for verification of accuracy prior to publication. Quotes and other information in multisource articles are subject to confirmation by their respective sources. The chief medical editor and the executive editor review all news and feature articles and have sole discretion as to the acceptance and rejection of material and final authority as to revisions deemed necessary for publication.

DISCLOSURE KEY. Financial interests are indicated by the following abbreviations:
C = Consultant/Advisor
E = Employee
L = Speakers bureau
O = Equity owner
P = Patents/Royalty
S = Grant support
For definitions of each category, see aao.org/eyenet/disclosures.

Letters

Asymmetric Glaucoma

I disagree with Dr. Cockerham's comment in "When It's Not Glaucoma" (Feature, November) that glaucoma is usually symmetric. The old Duke-Elder series on "simple glaucoma" states, "For one eye can be affected some considerable time before its fellow, it must be concluded that simple glaucoma is essentially a bilateral disease."[1] This asymmetry may be more pronounced in patients with normal-tension glaucoma.[1] Cataract, chronic open-angle glaucoma, and age-related macular degeneration are almost always a bit asymmetric and sometimes very asymmetric.

The big question is why are these three major age-related ocular diseases asymmetric? I have always had the suspicion that there is something wrong with the total ocular microcirculation in the eye with the worst disease severity (especially with cataracts). We need a functional metabolic scan of the retina to better understand such diseases. Optical coherence tomography only shows structural changes, which usually occur late in the course of a disease process.

Judson P. Smith, MD
Fort Worth, Texas

1 Drance SM et al. *Am J Ophthalmol.* 1968;65:891.

A Response

Dr. Smith's concerns are valid: Approximately 25% of patients with open-angle glaucoma have asymmetric disease (i.e., afferent pupillary defect [APD] is present, fields and OCT are dissimilar).[1,2] However, 75% or so do have symmetric disease. In this article, the point being made is that when signs are asymmetric—especially if intraocular pressures are symmetric and significant APD is present—symptoms and signs of another cause should be sought as well. One must ask the right questions and look carefully to fully confirm that the problem is truly glaucoma.

Kimberly Cockerham, MD, FACS
Stockton, Calif.

1 Schiefer U et al. *Br J Ophthalmol.* 2012;96(5):629-633.
2 Page CJ et al. *J Natl Med Assoc.* 1985;77(12):979-984.

GIVE OPHTHALMOLOGY A GREATER VOICE
Letters to the editor aren't the only way to be heard. If you know one of our newly elected Congresspeople, let the Academy know so we can update him or her on ophthalmic issues. In addition, you can get involved by working with a designated member of Congress on key topics. Visit aao.org/advocacy/action.

Opinion

RUTH D. WILLIAMS, MD

If You Build It, They Might Come

One of the persistent challenges for ophthalmology practices is finding, training, and retaining competent ophthalmic technicians. The medical department manager at our practice, Kati Read, oversees nearly 70 ophthalmic technicians, and she is chronically a few employees short.

The natural turnover among hourly wage employees, especially during the lowest unemployment rate in decades, contributes to the problem. In a survey of 1,200 young people in entry-level jobs, the *Harvard Business Review* found that half intend to leave within one year.[1] Kati reports that employees leave our practice to care for elderly parents, move to another state, return to school, or try out another career. They will also leave for a modest wage increase, even if the benefits aren't as robust. "It's most frustrating," she said, "when a well-trained technician leaves for another ophthalmology practice that offers $1 an hour more than we pay." It's also expensive to replace an employee.[2]

The reality is that there is a nationwide shortage of ophthalmic technicians. According to the Bureau of Labor Statistics, there are about 48,000 ophthalmic technicians in the United States.[3] That amounts to fewer than three technicians per practicing ophthalmologist.

Why is there a shortage? First, people who are interested in technical medical jobs might not think of ophthalmology. Indeed, career counselors at high schools and community colleges might promote medical technician training but not be aware of the opportunities within ophthalmology. Second, ophthalmology requires specific skills, and we typically don't draw employees from the much larger pool of medical technicians. Third, there aren't enough ophthalmic technician training programs. (In our case, the closest training program to our office used to be 45 minutes away. We occasionally had a trainee do a brief internship, but the students were not consistently exposed to our practice. Furthermore, they were mostly from towns closer to the training program and tended to take permanent jobs in that area.)

Dave Dopp, our ever-creative practice administrator, suggested we try to increase the numbers of qualified technicians in our region by collaborating with the local community college to establish an ophthalmic technician training program.

"It wasn't easy," Kati acknowledged. Illinois requires its state colleges to document that new programs are affordable and provide reasonable job opportunities. After approval by the College of DuPage's Health Sciences department, the training program was reviewed by the college board, a regional state college board, and, finally, the Illinois Community College Board. The process took nearly two years.

Kati and comprehensive ophthalmologist Michelle Andreoli developed the curriculum for an 18-month program of three courses, inelegantly titled Eye 1101, Eye 1102, and Eye 1103. Combined, the courses include 40 hours of classroom work and clinical training onsite in ophthalmology practices, after which the students are expected to be prepared to take the Certified Ophthalmic Assistant test. Tuition is $3,400. The program recently graduated its first class of seven ophthalmic technicians, and eight are enrolled in the second class.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Today, a beautiful brochure promoting the College of DuPage's health care–related training programs includes a description of the ophthalmic technician track. The brochure is made available to high school counselors and students interested in careers in health. We are hopeful that awareness of this career option will increase. As Michelle said, "Eye care is such a wonderful career. Our students acquire knowledge that ushers them into a profession that is meaningful, sustainable, and fun."

1 https://hbr.org/2017/12/how-to-improve-the-engagement-and-retention-of-young-hourly-workers. Accessed Nov. 13, 2018.

2 www.americanprogress.org/issues/economy/reports/2012/11/16/44464/there-are-significant-business-costs-to-replacing-employees/. Accessed Nov. 13, 2018.

3 www.bls.gov/oes/current/oes292057.htm. Accessed Nov. 13, 2018.

COMPLEX CASE MIX.

RENOWNED CLINICIANS.

DISTINGUISHED FACULTY.

GLOBAL ENGAGEMENT.

CUTTING-EDGE TECHNOLOGY.

DIVERSE SURGICAL TRAINING.

EYE-ONLY EMERGENCY ROOM.

MENTORSHIP AND CAMARADERIE.

Strength.

Voted #1 ophthalmology residency program
in the United States.*

Wills Eye Hospital

Believing is Seeing

BEST HOSPITALS U.S.News NATIONAL OPHTHALMOLOGY 2018-19

*Based on a Doximity clinical reputation survey for 2018-2019.

840 Walnut St., Philadelphia, PA 19107
willseye.org | 877.289.4557

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Save the Date

Mid-Year Forum 2019

Politics. Policy. Practice Management.

April 10 – 13 Washington, DC

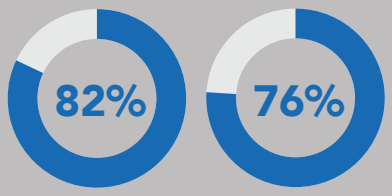
Where the Cornerstones of Ophthalmology and Business Come Together

Mid-Year Forum is one of the Academy's most significant yearly meetings, bringing the ophthalmology community together to drive change and shape our profession's future.

- Meet with federal lawmakers during Congressional Advocacy Day.
- Directly advocate for your profession and patients.
- Learn about changes that impact how you practice.
- Develop key strategies for successfully implementing new programs into your patient-care approach.
- Hear from expert panels on the future of our profession.
- Play a key role in driving the highest quality of care for your patients.

Registration Opens in January 2019.

aao.org/myf #myf2019



OMIC **Industry**

Reported claims without a payment

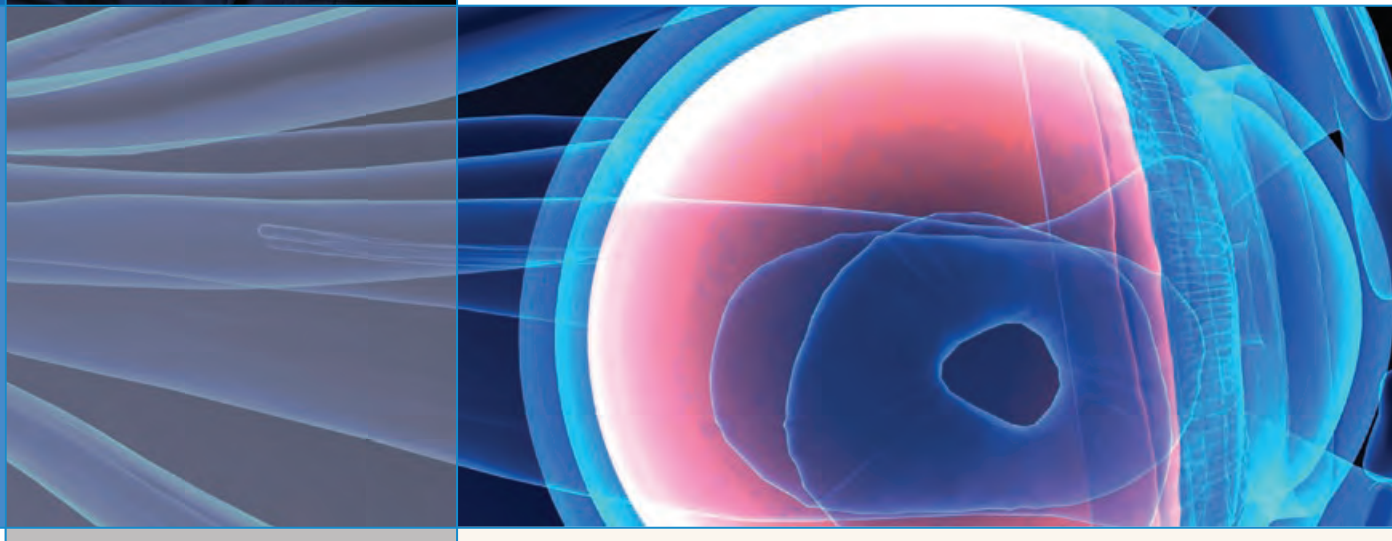
OMIC settles 25% fewer of the claims and lawsuits reported to us than our peer companies.

OMIC consistently outperforms multispecialty malpractice insurance companies in almost all claim defense results, benchmarks, and ratios used to evaluate performance in our industry.

OMIC makes a payment to the plaintiff is 25% fewer of the total claims reported vs. the traditional industry. When we do make a settlement, our average indemnity payment is 27% lower than the industry.

Our better claims experience is reflected in OMIC's superior operating performance, higher dividends, and lower rates.

Daniel Briceland, MD
Chair, Claims Committee



800.562.6642

www.omic.com/request-a-quote

OPHTHALMIC MUTUAL INSURANCE COMPANY
A Risk Retention Group

President's Statement

GEORGE A. WILLIAMS, MD

The Winds of Change

There is an aphorism that the pessimist complains about the wind, the optimist hopes the wind will change, and the realist adjusts the sails. My friends know that I am no sailor, but we all recognize that the winds of change are blowing across ophthalmology and all of medicine. At times, these winds seem to be coming from multiple directions: The federal government, state governments, commercial payers, employers, patients, and the media are demanding change in how physicians deliver and are paid for health care. How we handle these changes today will determine the future of our profession.

The challenges we face are many and diverse. In our daily operations, a byzantine regulatory morass imposed in the name of value and transparency steals time and resources from our practices and patients. Our treatment decisions are constrained and delayed by nebulous, often conflicting, preauthorization and step therapy requirements. Increasing drug prices for both established and new medications create financial hurdles for our patients. Complex rules for compounded drugs obstruct the supply of proven and often emergent therapies. Declining reimbursement and evolving coding policies threaten patient access. Private equity firms are knocking on our doors with the promise of riches, but without regard for our mission or our patients. Scope of practice battles are pushing the limits of reason—with legislation rather than education the mantra of nonphysician providers. Frustration with medical practice today is often palpable and is a primary driver in physician burnout.

Despite all of this, the field of ophthalmology has never been more exciting or promising. We stand on the threshold of a therapeutic wonderland that will diminish or prevent visual loss for generations to come. Already we have proof of principle in gene therapy for retinal dystrophies. Stem cells, improved prosthetics, neuroprotection, and optogenetics promise treatment for currently untreatable disease. Advances in microsurgical techniques will enhance our already-impressive success in ocular surgery. Further refinement of imaging technology will improve our perception of ocular disease. As remarkable as all these advances are, I suspect that they will be dwarfed by the impending revolution in artificial intelligence, which will make us all better doctors.

In this environment, the obvious question is how can we address our challenges and fulfill our promise to protect sight and empower lives? No doubt it will be difficult, but if our history is prologue, we can and will succeed. Since 1979, the Academy has been the epicenter of my professional development through education and advocacy. During this time, I have witnessed an unsurpassed dedication and sense of purpose in the thousands of Academy members who volunteer their time and amazing talents for the betterment of our patients. With your continued commitment to our patients and profession, the Academy stands ready to embrace our future.

George A. Williams, MD
Academy 2019 President

During my own volunteer experience as Secretary for Federal Affairs, I spent time in Washington, D.C., talking to members of Congress and the staff of two administrations about the potential and the pitfalls of the transition from a volume- to a value-based system. In a true value-based system, ophthalmology wins. What procedure in medicine has a 98+% success rate, costs Medicare under $2,000, restores function to the level of a teenager (or better), and typically lasts a lifetime? Modern cataract surgery! Whether it is cataract, glaucoma, retinal, pediatric, oculoplastic, or trauma surgery, what we do changes lives. So how do we keep federal focus on this incredible value?

The answer is simple: patient-centered data. No specialty has better data than the IRIS Registry (Intelligent Research in Sight), which demonstrates the value our services and procedures provide. As of Sept. 1, the IRIS Registry had over 200 million patient records across more than 52 million patients, making it the largest specialty society clinical data registry in the world. With your help, the Academy will use IRIS Registry to improve patient outcomes and demonstrate the value of ophthalmic care. Let the wind blow.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

OPHTHALMOLOGY JOB CENTER

Find the Right Fit Fast on the Only Job Site that Matters

Recruiting and retaining talented ophthalmic professionals is more challenging than ever. Find your best match quickly and more cost effectively through the Academy's Ophthalmology Job Center.

- **#1 recruiting site for ophthalmology**
- **The most listings for ophthalmologists**
- **Over 10,000 visitors per month**

Start your search today:
aao.org/jobcenter

"I've had great responses and saved over $30,000 in recruiters' fees by using the Academy's job site."

TONI CAMARATA JANSSON
HUMBOLDT PHYSICIANS SURGERY AND LASER CENTER

Protecting Sight. Empowering Lives.®

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Foundation

Join Tamara R. Fountain, MD, in Supporting Academy Programs

Become a Partners for Sight Donor

Make a bigger impact than you ever thought possible by giving to the American Academy of Ophthalmology Foundation at the Partners for Sight level ($1,000 – $2,499). Your support of Academy programs will help us educate more ophthalmologists and do even more good for patients worldwide.

Learn how $1,000 can make a difference at **aao.org/foundation/partners-for-sight**

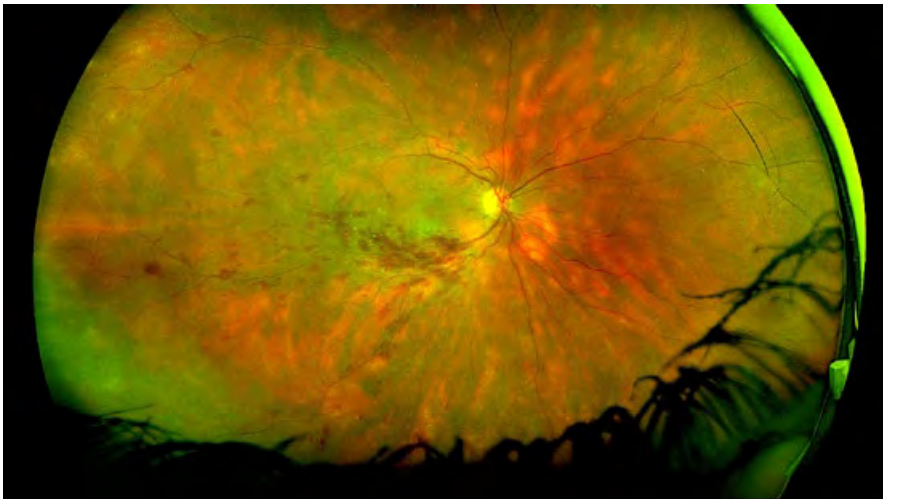
"I trust the Academy and I trust its leaders. When I pay dues, I support its core mission. When I give, I become part of a journey to make lives better around the world through the gift of sight. If you want to be a part of that, consider joining me. You just may get back more than you give."

TAMARA R. FOUNTAIN, MD
PARTNERS FOR SIGHT CHAMPION
NORTHBROOK, ILL.

Protecting Sight. Empowering Lives.®

UVEITIS

FDA Approves Insert for Chronic Posterior Uveitis



BIRDSHOT. *This ultra-widefield image is of a 45-year-old patient with central retinal vein occlusion and birdshot chorioretinopathy (HLA-A29+).*

AN INTRAVITREAL INSERT THAT slowly releases fluocinolone acetonide (FAi) to control inflammation associated with chronic, noninfectious posterior uveitis has been approved by the FDA. The novel drug delivery system was developed to break the treatment-quiescence-recurrence-treatment cycle that is a hallmark of the disease.

"For the first time, we'll have an injectable delivery system that can be implanted in the clinic and can release the drug for up to three years," said Glenn J. Jaffe, MD, at Duke University in Durham, North Carolina. Moreover, the implant will deliver "consistent dosing without the peaks and valleys [seen with] local corticosteroids," he said. Dr. Jaffe is lead author of a report on the 12-month safety and efficacy results of a phase 3 FAi clinical trial.[1]

A step forward. FAi, which will be brought to market under the brand name Yutiq (EyePoint Pharmaceuticals), builds on the strengths of earlier implants. Ozurdex (Allergan), an injectable insert containing 0.7 mg dexamethasone, lasts about three months, whereas Yutiq lasts up to three years. Retisert (Bausch + Lomb) is a long-lasting fluocinolone acetonide implant, but it requires surgical implantation, whereas Yutiq can be implanted via an in-office procedure.

Study specifics. Dr. Jaffe and his colleagues enrolled 129 people with recurrent noninfectious posterior uveitis. Subjects were randomly assigned to FAi (n = 87) or sham injection (n = 42). In the FAi group, 0.18 mg of the drug was delivered via the implant, which was injected through the pars plana into the vitreous cavity of the study eyes using a 25-gauge needle.

Recurrences. At 12 months, the FAi recurrence rate was significantly lower than that observed in the sham cohort (28% vs. 91%, respectively). The median time to first recurrence was 378 days in FAi eyes, compared to 70.5 days for sham eyes.

Recurrences were treated as needed. Through 12 months, 19% of the FAi group and 40% of the sham cohort had at least one adjunctive systemic treatment. Topical corticosteroid treatment was prescribed to 21% of FAi eyes and to 48% of sham eyes.

These findings confirmed what Dr. Jaffe had observed in 11 patients in an earlier study.[2] "What we saw was that the eyes remained quiet over a two-year period without recurrences. I was frequently able to get patients off systemic medications and drops without additional injections," he said.

Additional findings. Fewer FAi eyes lost 15 or more letters in best-corrected visual acuity (VA) than did sham eyes (14% vs. 31%, respectively). In addition, VA was preserved or improved more often with FAi.

With regard to intraocular pressure (IOP), FAi eyes were more likely to experience pressures greater or equal to 25 mm Hg or 30 mm Hg. More FAi eyes than sham eyes required IOP-lowering medication through 12 months, but the rate of surgical intervention was similar in the two cohorts.

Eyes treated with FAi were at greater risk of developing cataracts than were those in the sham cohort (33% vs. 12%, respectively). Of the 42 FAi eyes that were phakic at baseline, 14 (33%) required cataract surgery after 12 months.

Assessing risks and benefits. Although Dr. Jaffe did not downplay the cataract findings, he noted that cataracts are a known complication of uveitis treatment. "People on steroids

for a long enough period of time will eventually develop cataracts. I'd rather not have cataract, but if I can control the inflammation with an implant and keep patients seeing well, it's a worthwhile trade-off," he said.

As part of this assessment of risks and benefits, he referred to the implant's effect on recurrence rates, "which will help prevent secondary complications that can lead to vision loss."

—Miriam Karmel

1 Jaffe GJ et al. *Ophthalmology*. Published online Oct. 24, 2018.

2 Jaffe GJ et al. *Ophthalmology*. 2016;123(9):1940-1948.

Relevant financial disclosures—Dr. Jaffe: EyePoint Pharmaceuticals: C. This study was funded by EyePoint Pharmaceuticals; the sponsor participated in the design of the study, study conduct, data collection, data management, data analysis and interpretation, and preparation and review of the manuscript.

DRUG SIDE EFFECTS

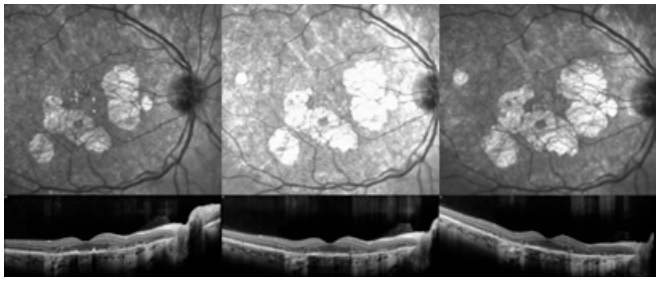
Urology Rx Linked to Maculopathy

RESEARCHERS AT EMORY UNIVERSITY report a unique maculopathy associated with chronic exposure to pentosan polysulfate sodium (PPS), a drug approved by the FDA in 1996 to treat discomfort associated with interstitial cystitis (IC).[1]

Previously unreported. The previously unreported maculopathy is thought to primarily affect the retinal pigment epithelium (RPE). It may be mistaken for other well-known macular disorders such as pattern dystrophy or age-related macular degeneration (AMD).

"Hundreds, if not thousands, of patients diagnosed with pattern dystrophy and AMD since the drug's approval may actually have a preventable drug-associated maculopathy," said senior author Nieraj Jain, MD, at Emory Eye Center in Atlanta.

Detective work. After seeing a string of patients with similar pigmentary macular changes and a past history of IC, the researchers culled their clinic's electronic medical records for PPS. Within the prior two years, six patients had previously been identified by the authors for an unknown pigmentary maculopathy. "That makes it one of the more common conditions that we saw in our clinic of hereditary retinal diseases," Dr. Jain said. (Since study publication in November 2018, the number of affected patients has grown to 15.)



EVIDENCE. *These images, taken over a two-year period in one patient, demonstrate the progressive nature of the patchy RPE atrophy noted in more severe cases of PPS-associated maculopathy.*

Findings of note. The new entity mimics hereditary pattern dystrophies, yet none of the patients had a family history of hereditary retinal degeneration, and none showed a pathogenic genetic mutation. Findings on fundus autofluorescence imaging were quite prominent, yet the fundus exam revealed only subtle paracentral hyperpigmentation at the level of the RPE, with surrounding pale yellow deposits.

Median exposure to PPS was 186 months; most patients reported trouble reading and experienced prolonged dark adaptation despite generally well-preserved visual acuity.

Clinical implications. "PPS-associated maculopathy has a permanent spot on our differential diagnosis for atypical pigmentary maculopathies," said lead author William Pearce, MD, at the Georgia Eye Institute in Savannah. "It is important that clinicians are aware of this association when evaluating patients with macular dystrophy or degeneration, as it could easily be overlooked due to the subtle findings."

Looking ahead. Dr. Jain stressed that causality must be confirmed. Nevertheless, he advises his affected patients to stop taking PPS. Should a cause and effect be determined, was there anything about the drug-approval process that could have prevented this? "Probably not, given that these patients were on the drug for years before manifesting visual symptoms," said Dr. Jain. "On the other hand, as pharmaceuticals become increasingly complex, we should recognize the vital role that clinicians play in the postmarket surveillance of novel therapies."

—Miriam Karmel

1 Pearce WA et al. *Ophthalmology*. 2018;125(11):1793-1802.

Relevant financial disclosures—Drs. Jain and Pearce: None.

NEURO-OPHTHALMOLOGY

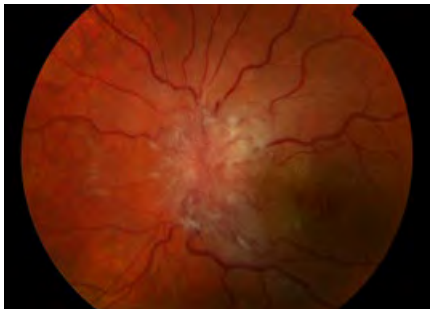
Burden of IIH Rising

BRITISH RESEARCHERS HAVE DOCUMENTED a sharp uptick in the number of cases of idiopathic intracranial hypertension (IIH) in England—and a concomitant rise in the costs of treatment.[1]

From Jan. 1, 2002, to Dec. 31, 2016, the incidence of IIH rose by 108%, and the number of hospital visits soared by 442%, the researchers found. "The overwhelming increase in patients diagnosed with IIH, and the amount of hospital visits over the study period, was surprising," said Susan P. Mollan, MBChB, FRCOphth, at University Hospitals Birmingham in the United Kingdom.

What sparked the study? "We had been tasked by the Association of British Neurologists to set up a special interest group that was multiprofessional to write practical guidelines on the management of IIH.[2] But there was little data showing the demographic shifts and [documenting] how patients were accessing care," Dr. Mollan said.

Findings. Dr. Mollan and her colleagues extracted data on hospital activity in England. After applying exclusion criteria, they confirmed that 23,182 new cases of IIH were diagnosed from 2002-2016, with an incidence of 2.26



PAPILLEDEMA. *Severe papilledema secondary to IIH in a young woman.*

per 100,000 in 2002, rising to 4.69 per 100,000 in 2016. The overall incidence was higher in women (7.7 per 100,000) than in men (1.6 per 100,000).

Treatment. Hospital admissions rose from 1,315 per year in 2002 to 7,123 per year in 2016. More than half the study cohort had a single hospital episode and no additional hospital care in the year following diagnosis. However, 37.8% had repeat hospital activity. Most patients (91.6%) were managed medically; 7.6% had a shunt procedure; 0.68% underwent bariatric surgery; and 0.07% underwent optic nerve sheath fenestration.

Costs. The cost of IIH-related hospital care climbed from £9.2 million to £49.9 million during the study period —and the researchers estimated that, if this trend continues, the cost will total £462.7 million in 2030.

More surprises. The researchers uncovered two additional surprises: For the first time, IIH in adults was associated with poverty and adverse obstetric outcomes. More than half of cases occurred in socioeconomically deprived areas, and pregnant women with IIH were more likely to undergo cesarean sections compared to pregnant women in the general population.

Wake-up call. Overall, the results confirm that the newly developed guidelines[2] are needed, Dr. Mollan said. "Better strategies for these patients are required when they access emergency care." *—Jean Shaw*

1 Mollan SP et al. *Eye.* Published online Oct. 24, 2018.
2 Mollan SP et al. *J Neurol Neurosurg Psychiatry.* 2018;89(10):1088-1100.
Relevant financial disclosures—Dr. Mollan: None.

RETINA

Mediterranean Diet Reduces Risk of Advanced AMD

THE MEDITERRANEAN DIET HAS BEEN FOUND TO lower the risk of cardiovascular disease and cognitive decline, but relatively few studies have examined its impact on age-related macular degeneration (AMD).

Now, a consortium of European researchers has found that the diet decreases an individual's risk of developing advanced AMD, particularly the dry form of the disease.[1] "We found that participants (55 years of age or older) who have a high adherence to the Mediterranean Diet have a 41% reduced risk of developing AMD," said lead author Bénédicte M.J. Merle, PhD, at the Université de Bordeaux in Bordeaux, France.

Rationale. The Mediterranean Diet provides an abundance of omega-3 fatty acids, lutein, and zeaxanthin, all of which have been found to contribute to retinal health, Dr. Merle pointed out. "The Mediterranean Diet is replete in healthful nutrient-rich foods, such as plant foods and fish. It also limits the consumption of unhealthful foods, such as red and processed meats and savory and salty industrialized products. So, we wanted to assess if patients who adhere to this diet have a reduced risk of developing advanced AMD."

In addition, she said, "We wanted to go further [than previous studies] by focusing on global nutrition rather than isolated nutrients."

Study specifics. Researchers with the EYE-RISK project (www.eyerisk.eu) investigated the associations between diet and incidence of advanced AMD in a large sample from two European population-based prospective studies, the Alienor Study and the Rotterdam Study 1 (RS-1). Participants in the Alienor Study (n = 550) were 73 years of age or older, and those in RS-1 (n = 4,446) were 55 or older; all were free of advanced AMD at baseline.

Dietary components. The researchers evaluated participants' adherence to the full Mediterranean Diet, using a nine-component score that assessed consumption of plant foods (fruits, vegetables, legumes, and cereals), fish, meat, dairy products, alcohol, and the ratio of monounsaturated-to-saturated fatty acids.

Outcomes. All told, 155 of the 4,996 participants developed advanced AMD during a mean follow-up of 9.9 years in RS-1 (range, 0.6-21.7 years) and 4.1 years in Alienor (range, 2.5-5.0 years). Those who hewed more closely to the Mediterranean Diet were less likely to develop AMD, despite any regional variations. (For instance, those in RS-1 were more likely to consume dairy, while those in the Alienor Study were more likely to eat vegetables, cereals, and fish.) "Participants from the Alienor and the RS-1 studies had slightly different diets, but the association with AMD incidence was similar [between the two cohorts]," Dr. Merle said.

The big picture. Of note, none of the individual food categories was associated with AMD incidence, which highlights the need to assess overall dietary patterns rather than individual components, the researchers said. Additional studies are planned, Dr. Merle said.

—Jean Shaw

1 Merle BMJ et al, for the EYE-RISK Consortium. *Ophthalmology*. Published online Aug. 13, 2018.
Relevant financial disclosures—Dr. Merle: Bausch + Lomb: C; Laboratoires Théa: S.

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Make Your Voice Heard on Key Issues That Impact Patient Care

Renew your Academy membership to support sound healthcare policy.

Amplifying your voice in Washington, D.C. — The Academy leads ophthalmology's efforts to prevent new administrative burdens and minimize the effect of penalties on your practice. No other ophthalmic organization has our deep relationships with leaders who shape guidelines for Medicare, the Department of Veterans Affairs and the F.D.A.

Protecting surgery by medically and surgically trained physicians — The Academy is actively fighting in every U.S. state and territory to ensure that eye surgery is the exclusive responsibility of surgeons.

Providing expert insight into the policies that affect your practice and patients — The Academy's experts provide leading analysis to help you understand how your practice is affected when federal agencies change and evolve the nation's myriad health policies.

Activate your benefits and renew your valuable membership today.
aao.org/benefits

Rep. Dave Loebsack (D-Iowa), left, met with Academy Advocacy Ambassador Philip I. Niles, MD, MBA, during Mid-Year Forum 2016's Congressional Advocacy Day. This in-person advocacy allows attendees to directly interface with federal lawmakers on behalf of ophthalmology's patients, discussing topics such as fair Medicare physician reimbursements, relief from administrative burdens, and preserving access to sight-saving compounded drugs.

Protecting Sight. Empowering Lives.®

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

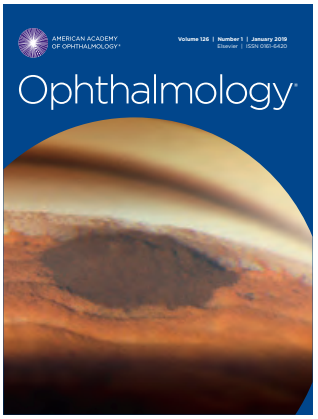
Ophthalmology

Selected by Stephen D. McLeod, MD

Schlemm Canal Microstent in Patients With POAG and Cataract

January 2019

Samuelson et al. compared the safety and effectiveness of cataract surgery alone versus the Hydrus microstent (Ivantis) in conjunction with cataract surgery. They found that the combination was more effective at lowering intraocular pressure (IOP) by month 12 and month 24. Safety findings for the study groups were similar.



Enrollees of this single-masked trial had concomitant primary open-angle glaucoma (POAG), visually significant cataract, and washed-out modified diurnal IOP (MDIOP) ranging from 22 mm Hg to 34 mm Hg. After uncomplicated phacoemulsification, patients were assigned randomly (2:1) to receive either a single Hydrus microstent in the Schlemm canal or no stent. Comprehensive eye exams were performed at eight postoperative points, from the first day following surgery to month 24. Medication washout and MDIOP measurements were repeated at 12 and 24 months. The primary measure of effectiveness was the proportion of subjects with a reduction of at least 20% in unmedicated MDIOP. The secondary measure was the change in mean MDIOP from baseline.

Use of topical medication for hypotension was tracked throughout follow-up. Safety measures included the frequency of surgical complications and the occurrence of adverse events.

After phacoemulsification, 369 eyes received the microstent and 187 did not. By month 24, unmedicated MDIOP had declined by ≥20% in 77.3% of the stent-treated group and in 57.8% of the control group. The mean reduction in unmedicated MDIOP from baseline to 24 months was –7.6 mm Hg in the stent-treated group and –5.3 mm Hg in the control group. The mean number of medications declined from 1.7 at baseline to 0.3 by 24 months in the stent group and from 1.7 to 0.7 in the control group. (All p values < .001.) No serious ocular adverse events were associated with the microstent. Overall, safety findings were similar for the study groups. The microstent group had a higher rate of focal adhesions, and the control group had more IOP-related complications.

The authors recommend that long-term head-to-head studies be performed to better understand the efficacy and safety of microstent implantation and to compare this adjunct with other novel minimally invasive devices.

Low-Dose Atropine to Control Myopia Progression

January 2019

Low-concentration atropine is a new treatment for myopia progression, but its efficacy and optimal concentration are uncertain. In a large double-masked trial, **Yam et al.** compared efficacy and safety between eyedrops containing low amounts of atropine (0.05%, 0.025%, or 0.01%) and placebo eyedrops. They noted a concentration-dependent effect for the reduction of myopia progression. All doses were well tolerated and had no adverse effect on vision-related quality of life. The highest concentration (0.05%) proved the most effective for controlling spherical equivalent (SE) progression and axial length (AL) elongation in their one-year study.

This randomized placebo-controlled study included 438 children between the ages of 4 and 12 who had myopia of at least –1.0 D and astigmatism of –2.5 D or less. Patients were assigned randomly (1:1:1:1) to receive atropine eyedrops (0.05%, 0.025%, or 0.01%) or control drops, which contained sodium chloride. Drops were applied nightly for a full year. Accommodation amplitude, AL, best-corrected visual acuity, cycloplegic refraction, and pupil diameter were measured at five points (baseline, week 2, and months 4, 8, and 12). A visual function questionnaire was administered at the one-year visit. Main outcomes were changes in SE and AL. A generalized estimating equation was used to compare findings.

At one year, mean SE had changed

by –0.27 D, –0.46 D, –0.59 D, and –0.81 D in the 0.05%, 0.025%, and 0.01% atropine groups and the placebo group, respectively. The corresponding mean increases in AL were 0.20 mm, 0.29 mm, 0.36 mm, and 0.41 mm. Accommodation amplitude was reduced by 1.98 D, 1.61 D, 0.26 D, and 0.32 D, respectively. The increases in pupil size under photopic and mesopic conditions (respectively) were 1.03 and 0.58 mm in the 0.05% atropine group, 0.76 and 0.43 mm in the 0.025% atropine group, 0.49 and 0.23 mm in the 0.01% atropine group, and 0.13 and 0.02 in the placebo group. (All p values < .001.) Visual acuity and vision-related quality of life were not impaired in any group.

More phases of the study are planned to assess the durability and longevity of these effects. After the second phase, the authors will report two-year efficacy and safety findings for the three concentrations of atropine. Subsequently, the researchers will assess the viability of discontinuing treatment once the myopia progression has been controlled, and atropine will be resumed in appropriate cases. *(Also see related commentary by Padmaja Sankaridurg, PhD, in the same issue.)*

DMEK Versus Ultrathin DSAEK for Corneal Endothelial Dysfunction

January 2019

Results of nonrandomized and observational studies have suggested that visual outcomes are similar for Descemet membrane endothelial keratoplasty (DMEK) and ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK). However, the study designs have hindered direct comparisons. To permit a more meaningful comparison of these procedures, **Chamberlain et al.** conducted a randomized controlled trial to evaluate visual outcomes and complication rates. They found that DMEK yielded superior visual acuity during the year following surgery, although complication rates were similar for the two procedures.

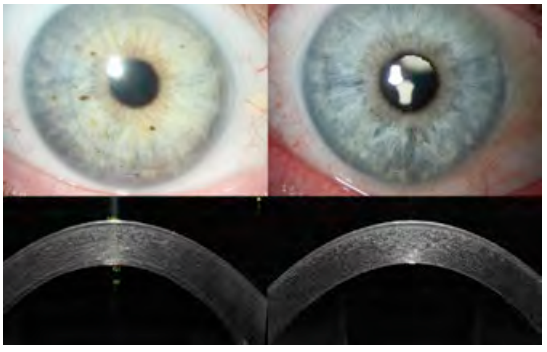
Eligible participants had damaged or diseased endothelium (from Fuchs endothelial dystrophy or pseudophakic bullous keratopathy). Within two days prior to surgery, eyes were assigned randomly to receive DMEK or UT-DSAEK. Standardized surgical techniques were used. Patients were masked as to their intervention and received the same postoperative instructions. Moreover, the refractionist who assessed visual outcomes was unaware of each patient's procedure. The primary outcome was best spectacle-corrected visual acuity (BSCVA) at six months. Secondary outcomes were BSCVA at the three- and 12-month marks, intra- and postoperative complications, endothelial cell counts, and change in pachymetry.

Of the 216 patients with endothelial dysfunction who were screened, 38 (50 eyes) were enrolled. After the researchers corrected for baseline VA, DMEK was found to result in better visual outcomes. BSCVA was 1.5 lines better for the DMEK group at three months, 1.8 lines better at six months, and 1.4 lines better at 12 months. At six months, the average endothelial cell count was 1,963/mm^2 in the DMEK group and 2,113/mm^2 in the UT-DSAEK group. At 12 months, the average cell counts were 1,855/mm^2 and 2,070/mm^2, respectively.

Rates of intra- and postoperative complications were comparable for the study groups.

The authors noted that DMEK—when performed by experienced surgeons—appears to elicit better visual outcomes and faster recovery than UT-DSAEK. They emphasized that larger multicenter trials may help to clarify the dissimilar outcomes. *(Also see related commentary by Marianne Price, PhD, in the same issue.)*

—Summaries by Lynda Seminara



COMPARISON. *Clinical photographs and OCT images from patients who underwent UT-DSAEK (left) and DMEK (right).*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Predictors of Postinjection Endophthalmitis

January 2019

Stem et al. set out to determine the incidence of endophthalmitis following anti-VEGF injections and to identify potential ways of lowering that risk. They found that the overall incidence of postinjection endophthalmitis was low—and that the use of lidocaine jelly or TetraVisc (tetracaine) may be associated with an increased risk.

For this retrospective single-center study, the authors assessed all patients in their practice who received an intravitreal injection of an anti-VEGF drug between Jan. 1, 2014, and March 31, 2017. All told, 154,198 intravitreal injections were given during this time, and 58 cases of endophthalmitis occurred, for a rate of 1:2,659. Less than half of these cases (24; 41%) were culture-positive.

A number of risk factors were evaluated, including povidone-iodine (PVI) solution strength and the choice of anti-VEGF drug. No difference in endophthalmitis rates emerged among the anti-VEGF drugs (aflibercept, bevacizumab, and ranibizumab 0.3 mg and 0.5 mg). Moreover, the prophylactic use of 10% PVI neither reduced nor increased the risk of endophthalmitis relative to the use of a 5% PVI solution. In addition, no association emerged regarding several other potential risk factors, including lid speculum use, choice of injection site, or conjunctival displacement.

However, both 2% lidocaine jelly and 0.5% TetraVisc emerged as independent risk factors. As the authors noted, this finding has not previously been reported and merits further investigation. *—Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

What Degree of Visual Field Damage Causes Disability for Glaucoma Patients?

January 2019

Jammal et al. used latent class analysis (LCA) to classify patient-reported glaucoma outcomes and to quantify the amount of visual field damage that results in disability. They found that this model, which is rarely used in ophthalmology, is useful for both purposes, and they noted that early visual field loss in the better eye can cause substantial disability.

Participants in this cross-sectional study were required to have open angles on gonioscopy. The 263 enrollees completed the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), after which an LCA model was applied to analyze the data. Patients were grouped into mutually exclusive classes according to questionnaire responses. Differences between the classes were documented, including standard automated perimetry mean deviations (SAP MD) and integrated binocular mean sensitivity values. The optimal number of classes was defined based on goodness-of-fit criteria, interpretability, and clinical utility.

The model containing two latent classes (disabled and nondisabled) had the best fit, demonstrating Lo-Mendell-Rubin test values superior to those of the one-class model and not significantly different from those of models with more classes. The two-class final LCA model had a high entropy value (0.965), denoting excellent distinction between the classes. Forty-eight patients (18%) were classified as disabled, and 215 (82%) were classified as nondisabled. The average SAP MD of the better eye was –5.98 dB in the disabled group and –2.51 dB in the nondisabled group ($p < .001$). Corresponding values for the worse eye were –13.36 dB and –6.05 dB ($p < .001$).

This study showed that damage of approximately –6 dB for SAP MD, denoting relatively early visual field loss, may signal significant disability if present in the better eye. The research suggests that LCA may be a valuable tool to analyze patients' concerns about quality of life.

High-Dose Gene Therapy and BCVA in Choroideremia

January 2019

In a two-year clinical trial, **Lam et al.** looked at the safety and efficacy of high-dose gene therapy in patients with choroideremia. Their findings demonstrated that the treatment is safe and potentially effective and that best-corrected visual acuity (BCVA) may be an appropriate outcome measure for monitoring the progression of choroideremia.

The authors reported 24-month findings of their phase 2 clinical trial. Six men (32-72 years of age) with advanced choroideremia underwent subfoveal injection of adeno-associated virus 2 capsids that harbored a transcript encoding Rab escort protein 1 (i.e., AAV2-REP1; 1011 genome particles in 0.1 mL). The eye with worse visual acuity was treated, and the untreated fellow eye served as the control. Injection of vector was performed slowly, guided by microscope-integrated optical coherence tomography.

The primary outcome measure was change in BCVA from baseline. Secondary endpoints included changes in central visual field (by microperimetry), color vision, contrast sensitivity, and fundus autofluorescence. To assess safety, adverse events and immunologic parameters were recorded, including viral shedding and vector antibody responses.

The baseline mean BCVA was 65.3 ± 8.8 letters in treated eyes and 77.0 ± 4.2 letters in untreated eyes. Two years after therapy, the changes from baseline ranged from −1 to +10 letters in treated eyes and −2 to +4 letters in untreated eyes. No eye had a substantial change in microperimetry findings, color vision, or contrast sensitivity; all eyes (treated and control) had progressive shrinkage in areas of fundus autofluorescence. No serious adverse events were noted, and the immunologic profiles were favorable. In two patients, an atrophic retinal hole developed in a nonfunctioning macular area.

This slow-injection technique of high-dose gene therapy appears to be safe and may permit maintenance, or even improvement, of BCVA in patients with choroideremia. The fact that no untreated study eye had significant improvement in BCVA suggests that BCVA is a suitable primary outcome measure for future choroideremia trials. The authors acknowledged that larger studies are needed to confirm the promising results. *(Also see page 26.)*

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Cadmium Exposure Increases Risk of Contrast Sensitivity Impairment

December 2018

Paulsen et al. set out to determine the incidence of and factors associated with deficits in contrast sensitivity (CS). They found that CS impairment was linked to smoking and blood levels of cadmium, but not to lead levels.

For this study, the authors included patients from the Beaver Dam Offspring Study who had normal CS in both eyes at baseline. Participants were between the ages of 21 and 84, and baseline data were gathered from June 2005 through early August 2008. Two follow-up exams occurred subsequently at five-year intervals. CS testing was assessed with Pelli-Robson letter sensitivity charts. Incident impairment was defined as a log CS score <1.55 in either eye at a follow-up exam. Levels of cadmium and lead were measured in whole blood by using inductively coupled plasma mass spectrometry. Associations between baseline characteristics and CS impairment were evaluated using Cox proportional hazard models and were expressed as hazard ratios (HR) and 95% confidence intervals (CI).

The mean age of participants (N = 1,983) was 48 years; 52% were female. The 10-year cumulative incidence of CS impairment was 24.8% (95% CI, 22.9-

26.8) and was similar for men (24.6%) and women (24.9%). It was highest (66.3%) in the oldest participants (65-84 years). Factors linked to greater risk of CS impairment were cadmium level in the highest quintile (HR, 1.35; 95% CI, 1.02-1.78), older age (HR, 1.36; 95% CI, 1.25-1.47), and plaque sites (four to six sites: HR, 2.75; 95% CI, 1.26-6.05; one to three sites: HR, 1.43; 95% CI, 1.07-1.92). Other contributors were impaired visual acuity (HR, 3.61; 95% CI, 1.61-8.10), cataract (HR, 1.99; 95% CI, 1.21-3.28), and larger waist circumference (HR, 1.06; 95% CI, 1.01-1.11). Factors denoting lower risk were male sex (HR, 0.77; 95% CI, 0.60-0.98) and any alcohol consumption in the last year (HR, 0.61; 95% CI, 0.43-0.88). When cadmium exposure was replaced with smoking status in these models, the findings were similar. Lead level did not affect risk.

Many of the identified risk factors are modifiable, which may imply that changes in lifestyle could reduce the risk of CS impairment. Weight loss and efforts to improve vascular health also may be beneficial. *(Also see related commentary by Xiang Li, PhD, in the same issue.)*

Use of Deep Learning to Estimate Five-Year Risk of Advanced AMD

December 2018

Burlina et al. applied deep learning (DL) to fundus images from the Age-Related Eye Disease Study (AREDS) to automatically assess the severity of age-related macular degeneration (AMD) and estimate the five-year risk of progression to advanced-stage AMD. They found that the DL model's performance was comparable to that of humans when the AREDS 4-step severity scale was used. Promising results were achieved with the AREDS 9-step severity scale (which normally requires highly trained graders) as well as for estimating five-year risk of progression.

For their study, the authors gathered information from the AREDS dataset to develop deep convolutional neural networks that were trained to provide detailed automated AMD grading. Algorithm performance was compared with results from a human grader and against a criterion standard (gradings from a fundus photograph reading center). Three methods for estimating five-year risk were developed: hard, soft, and regressed. Main outcomes were weighted κ scores and mean unsigned errors for estimating five-year probability of progression to advanced AMD. The study included 67,401 color fundus images from a total of 4,613 patients.

Analysis showed a weighted κ score of 0.77 for the 4-step scale and 0.74 for the 9-step scale. The overall mean estimation error for 5-year risk ranged from 3.5% to 5.3%. The error was smaller for lower-risk classes. Of the three methods, hard prediction performed best for all classes except those in which the soft prediction outperformed all and in which the regressed prediction outperformed all.

The authors noted the large imbalances among some of the severity classes: For instance, for the 9-step scale, 24,411 images were classified as step 1, and 1,160 images were classified as step 3. Nonetheless, they said, DL has the potential to assist physicians with detailed risk assessment and evaluation of disease progression during treatment. *(Also see related commentary by Harpal S. Sandhu, MD, FRCSC, Ayman El-Baz, PhD, and Johanna M. Seddon, MD, ScM, in the same issue.)*

Is It Time to Narrow the Criteria for ROP Screening?

December 2018

Current guidelines for detecting retinopathy of prematurity (ROP) in the United States include a wide range of birth weights and gestational ages and thus may entail unnecessary evaluation of infants who are at low risk for ROP. **Quinn et al.** examined data from the Postnatal Growth and ROP (G-ROP) study to discern the incidence, timing of onset, and early course of ROP. Of those who received serial ROP exams, 43.1% developed ROP, and 12.5% developed severe ROP. Nearly all of those affected by severe ROP weighed less than 1,251 g at birth.

This study was conducted at 29 hospitals in North America (from 2006-2011) and included 7,483 infants. Mean birth weight was 1,099 g. The most severe ROP in either eye was classified as none, mild, type 2, or type 1, according to criteria of the Early Treatment for ROP Study. Other documented data were postmenstrual age at ROP onset, stage of ROP, and treatment given.

ROP occurred in 3,224 infants (43.1%), with type 1 disease developing in 459 (6.1%) and type 2 disease in 472 (6.3%). Roughly 98% of those with type 1 or 2 ROP had a birth weight <1,251 g. Of the babies born at ≤24 weeks' gestation, severe ROP developed in 49.5%. Of those born after 30 weeks who weighed >1,501 g at birth, only four (0.75%) had severe ROP. Treatment was given to 514 infants (6.9%), in one or both eyes. Zone I disease was present in 147 infants (2%). Only about half the eyes (49.4%) had vascularization into zone III by 37 weeks' postmenstrual age.

Unlike other large studies, this research included all infants who were eligible for ROP screening. Although ROP was present in more than 40% of "at-risk" premature infants, most cases did not require treatment. The lower-risk profile noted for larger babies supports efforts to improve the specificity of risk assessment and raise the possibility of a revision of the criteria that warrant examination for ROP. *(Also see related commentary by Amy K. Hutchinson, MD, in the same issue.)*

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Favorable Vision Effects of Retinal Gene Therapy for Choroideremia

Nature Medicine
2018;24:1507-1512

Choroideremia is a chronic X-linked retinal degeneration that leads to blindness because of deficiency in the Rab escort protein 1 (REP1). **Xue et al.** designed an adeno-associated viral vector to express REP1 and then evaluated it in a gene therapy trial during which it was injected into patients with choroideremia. Compared with control

eyes, and despite complications in two patients, the treated eyes had substantial improvement in visual acuity (VA; 4.5-letter gain vs. 1.5-letter loss). Moreover, the treatment was well tolerated.

The two-year study was conducted at Oxford Eye Hospital and included 14 patients. All participants were male (age range, 25-73 years) and had confirmed null mutations of the *CHM* gene. Each patient received a single subretinal injection of a virus containing the missing gene. The injection was administered to one eye of each patient; the untreated fellow eye served as the control. The primary endpoint was vision change from baseline to two years in treated versus untreated eyes.

Initially, 12 patients were enrolled. However, complications in two patients (related to vector administration) led to a 24-month delay and a protocol change to improve the surgical technique and immune-suppression regimen. The ethics committee approved an extension of the trial, including recruitment of two additional patients, so that 12 patients would receive the per-protocol therapy and follow-up, as originally planned.

The gain in vision was at least 1 line in six treated eyes and at least 3 lines in three treated eyes. In general, the VA gains and recovery occurred within six months of the treatment. Small gains in VA were noted for eyes with end-stage choroideremia, which otherwise would have declined rapidly. Longer follow-up, up to five years for some patients (mean, 3.6 years), confirmed that the improvements had been maintained.

The findings suggest that a single treatment with a single gene may be sufficient to prevent blindness and, perhaps, ultimately cure other debilitating genetic conditions. *(Also see page 25.)*

Myo-Inositol Lacked Efficacy and Safety in a Multicenter Trial

JAMA
2018;320(16):1649-1658

In studies of preterm infants with respiratory distress, *myo*-inositol appeared to reduce the severity of retinopathy of prematurity (ROP) and the frequency of ROP, death, and intraventricular hemorrhage. However, its efficacy and safety had not been tested in large trials until a recent multicenter study by **Phelps et al.** In their large population of infants, *myo*-inositol did not reduce the risk of death or type 1 ROP relative to placebo, suggesting that it is not a viable treatment for this age group. The study was terminated early because the mortality rate was significantly higher in the *myo*-inositol arm.

This randomized trial included 638 infants (gestational age [GA] <28 weeks) who were enrolled from 18 U.S. neonatal intensive care centers in 2014 and 2015. (The planned enrollment was 1,760 participants, which would have been sufficient to detect an absolute reduction in death or type 1 ROP of 7% with 90% power.)

Participants received either *myo*-inositol 40 mg/kg (n = 321) or placebo (n = 321) for up to 10 weeks. Administration was every 12 hours, intravenously and then enterally (when feeding). The main outcomes were type 1 ROP or death before the determination of an unfavorable ROP status. The designated favorable outcome was survival without type 1 ROP. The final month of follow-up was February 2016.

In the study population (mean GA, 26 weeks; 50% male), 92% had a documented outcome. Death or type 1 ROP occurred more frequently in the *myo*-inositol group (29% vs. 21%; adjusted relative risk, 1.41; p = .01). Before 55 weeks' postmenstrual age, death (any cause) had occurred in 18% of the *myo*-inositol group and 11% of the placebo group (adjusted relative risk, 1.66; p = .007). The most common serious adverse events with active treatment versus placebo, respectively, were systemic infection (16% vs. 11%), respiratory distress (15% vs. 13%), intraventricular hemorrhage (10% vs. 9%), poor perfusion or hypotension (7% vs. 4%), and necrotizing enterocolitis (6% vs. 4%).

Although these findings do not support the efficacy or safety of *myo*-inositol in premature infants, the trial's early termination does not allow for definitive conclusions.

—Summaries by Lynda Seminara

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Sometimes Google Isn't Good Enough and PubMed Isn't Practical

Turn to the reference that is vetted by 100 ophthalmologists every year.

The **BCSC**® is your definitive source in an ever-expanding universe of clinical information.

Update your complete Basic and Clinical Science Course™ set. Visit aao.org/bcsc

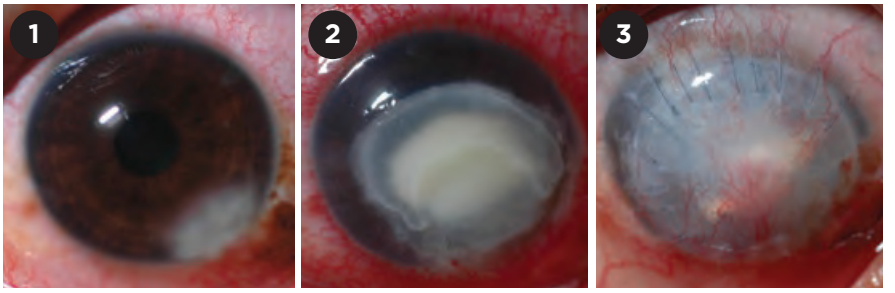
Protecting Sight. Empowering Lives.®

New Gains With Fungal Keratitis

Fungal keratitis is notoriously challenging to diagnose and treat, and aggressive cases can perforate through the cornea and spread inside of the eye, making early diagnosis critical. "The keys to being able to successfully manage these cases are first having the suspicion of a fungal infection, then being able to confirm the diagnosis quickly," said Bennie H. Jeng, MD, at the University of Maryland School of Medicine in Baltimore.

"Current management is still based on figuring out that it's fungus as quickly as possible and using traditional antifungal treatment, which includes topical natamycin," said Thomas M. Lietman, MD, at the University of California, San Francisco (UCSF). But topical natamycin penetrates poorly into the corneal stroma, making deep ulcers hard to treat,[1] and a new "wonder drug" for fungal keratitis remains elusive, Dr. Leitman said. In the Mycotic Ulcer Treatment Trials (MUTT) I and II, even the newest drug, voriconazole, failed to show significant benefit, either in outperforming topical natamycin (in MUTT I) or as an adjuvant oral therapy to antifungal topicals (in MUTT II), he said.

Fortunately, there are some bright lights on the horizon: Metagenomic deep sequencing (MDS) and repeat cultures raise the promise of an earlier diagnosis. And corneal cross-linking (CXL) may improve treatment outcomes.



PROGRESSION. *This patient's ulcer was culture-positive for Fusarium. At enrollment in MUTT I (Fig. 1), his VA was 20/25; after three weeks of topical voriconazole, his VA had declined to hand motions (Fig. 2). He experienced perforation and required a TPK, and at three months (Fig. 3), his VA was light perception.*

Devastating Infections

"These devastating fungal infections are very difficult to treat," said Jennifer Rose-Nussbaumer, MD, also at UCSF. "In one of our studies, we gave patients everything we had: eyedrops, oral medications, and surgery—and about 50% still needed therapeutic penetrating keratoplasty [TPK]."

Diagnostic challenge. A key issue with fungal keratitis is the time lag to an accurate diagnosis. "We always jump to thinking about the best way to treat fungal keratitis," Dr. Lietman said, "but if patients are not coming in for two or three weeks and the damage is already done, then early diagnosis is where we're going to make a big leap forward."

With a fungal infection of the cornea, the corneal epithelium is often intact, so the infection is harder to catch with traditional cultures. And, as fungus can occur in a wound and penetrate deeper into the cornea, it's less amenable to the scraping techniques used for bacteria. Moreover, the rate of culture-positive scraping is low, even in academic settings.

"I am at a tertiary center, and we sometimes only see the infection once it has resulted in a corneal melt," said Zaina N. Al-Mohtaseb, MD, at Baylor College of Medicine in Houston. "Many referral physicians don't have the capabilities we have at academic institutions [e.g., a good microbiology lab and confocal microscopy]. But even with these, the sensitivity and specificity of these tests for fungal keratitis is low."

Treatment attempts. Furthermore, attempted treatment can backfire. "Given the difficulty with diagnosis, some of the patients sent to our practice are on multiple therapies, such as antibacterials, antivirals, and steroids," said Dr. Al-Mohtaseb. "Unfortunately, these can

BY REBECCA TAYLOR, INTERVIEWING **ZAINA N. AL-MOHTASEB, MD, BENNIE H. JENG, MD, THOMAS M. LIETMAN, MD,** AND **JENNIFER ROSE-NUSSBAUMER, MD.**

Austin A. et al. *Ophthalmology.* 2017;124(11):1678-1689.

worsen the infection—especially the topical steroids." As a result, she said that she has had to re-culture some patients. "Others have needed a corneal biopsy for diagnosis, and, at times—although this is rare—the diagnosis occurs after a TPK."

Dr. Jeng also pointed out that "different fungi may respond differently to the various antifungal medications. Personally, my go-to antifungal for Candida is amphotericin B, which needs to be extemporaneously compounded."

Dr. Mohtaseb added, "Cases that result in corneal perforation or fail to progress despite maximal appropriate antifungal therapy might require TPK to prevent scleral involvement and endophthalmitis and to preserve the globe." With regard to therapeutic grafts, she said, "the risk of recurrence is as high as 50%[2]—so, again, early diagnosis and treatment is of utmost importance."

Improving Diagnosis

Metagenomic deep seqencing. MDS is at the cutting edge of new diagnostic technology for fungal corneal ulcers. With a targeted test like polymerase chain reaction (PCR), clinicians must know what they're looking for. In contrast, MDS is considered unbiased, as it will identify any organism in the clinical sample.

"With next-generation sequencing, the gain is in quicker, more accurate diagnosis because we don't have to wait for the fungus to grow," said Dr. Lietman. "MDS can tell us whether it's a bacteria, a fungus, a parasite like Acanthamoeba, or another organism. This should allow for very rapid diagnosis."

Clinical benefit. "Sequencing technology is being used more and more to help clinicians make diagnoses, and in the setting of fungal infections, this technology has huge potential in making a positive clinical impact," said Dr. Jeng.

Scientific benefit. "The technology is also scientifically interesting for us because there are new organisms we didn't know that cause keratitis," Dr. Lietman said. As a result, he said, "next-generation sequencing is good for pathogen discovery."

Not FDA approved. However, it should be noted that MDS is neither approved nor in mainstream use. Once it is, the hope is that any ophthalmologist will be able to take a swab, preserve it in nucleic acid–stabilizing media, and ship it off to a lab. The sample will be sequenced, and the treating clinician will get the results faster than the cultures could grow.

Repeat cultures. Another new diagnostic—and prognostic—tool is the use of repeat cultures after initiating treatment.

"A really interesting subfinding of MUTT I and II came from repeat cultures at six days," said Dr. Rose-Nussbaumer. "If patients were positive on that repeat culture, they had a much higher risk of going on to need surgery, having worse three-month visual acuity, and having a larger scar size. It correlated with every single negative outcome."

Identifying TPK need. Repeat cultures identified patients who would ultimately need TPK, said Dr. Rose-Nussbaumer. "In MUTT II, we found that the vast majority of patients who met certain criteria, such as large ulcers that were deep and culture positive, needed TPK. Repeat cultures are a very useful tool for prognosis and helping identify patient populations, such as those who might benefit from a TPK early on when the chances of eliminating the infection are higher."

Adapting treatment. When six-day repeat cultures are positive, clinicians can increase the drug dosage, add a different topical antifungal, try an oral antifungal, and more closely monitor patients who are at higher risk of corneal perforation or may need TPK to excise the infection.[3]

Use of repeat cultures also helps determine which antimicrobials are working.[4] "If we only use healing time or vision as outcomes, we don't have much hope of distinguishing different antimicrobial agents," Dr. Lietman said. In contrast, he said, "repeat cultures are an excellent way to distinguish new antimicrobials, because we're directly testing how well we killed the fungus. And the fact that six-day culture correlates with vision gives more credibility to using repeat cultures in future clinical trials."

New Use of CXL?

Although CXL has been well studied for ectasia, "it hasn't been very well studied as a useful adjuvant for people with infections and corneal ulcers," said Dr. Rose-Nussbaumer.

After the MUTT II trial, Dr. Rose-Nussbaumer said, she went back to look at patients' charts, and many needed multiple surgeries. "The fungal infection came back, or they had a retinal detachment; it looked like almost all those eyes were lost. That's why we started looking at cross-linking as a potential therapy for fungal keratitis: We've run out of medical therapies, and intrastromal injection of antifungals doesn't really work."

CLAIR trial. Dr. Rose-Nussbaumer's current trial, Cross-Linking–Assisted Infection Reduction (CLAIR), is now in its follow-up phase. "We randomized patients to medical therapy alone versus medical therapy and adjuvant CXL," she said. "We enrolled 111 patients with moderate fungal keratitis, and our primary outcome measure will be culture positivity after CXL." The researchers will also look at clinical measures such as visual acuity, scar size, the need for TPK, and other complications.

CXL caveats. There are still unknowns in using CXL to treat corneal infections. It's possible, for instance, that CXL "has an antiseptic quality that treats the infection but also causes a lot of abnormalities in the shape of the cornea that could negatively affect vision," Dr. Rose-Nussbaumer hypothesized. "For patients with keratoconus, for instance, we counsel that they may lose a line of best-corrected vision after CXL, because some opacity could form in the cornea that might be a result of cross-linking."

Evolving Epidemiology

In the United States, fungal keratitis is most often seen in warm, humid regions. "Some of the most devastating infections that I saw in Miami and now see in Texas are due to fungal keratitis," Dr. Al-Mohtaseb said.

There is some speculation that cli-

mate change may be driving an increase in fungal ulcers, as they tend to occur in patients who live in tropical areas. "In these areas, filamentous fungi such as Fusarium predominate," said Dr. Jeng.

However, he added, "Even in temperate areas of the world, fungal keratitis is still seen, and it needs to be suspected in certain cases." In temperate climates, he noted, "yeasts such as Candida are most frequently seen. In either case, successful treatment of fungal keratitis still depends on accurate and timely diagnosis."

What about bacterial keratitis? "Bacterial ulcers seem to be becoming less common because people can quickly access antibiotic drops anywhere in the world," Dr. Lietman said. Given the prevalence of antibiotics, by the time a patient comes to the doctor's office, the bacteria may already be dead. "That may be why, from the ophthalmologists' perspective, the ulcers they see—particularly in tertiary settings—are often not bacterial; they're now often fungal or Acanthamoeba infections."

1 Austin A et al. *Ophthalmology*. 2017;124(11):1678-1689.
2 Sharma N et al. *Curr Opinion Ophthalmol.* 2010;21(4):293-300.
3 Ray KJ et al, for the Mycotic Ulcer Treatment Trial Group. *Am J Ophthalmol.* 2017;178:157-162.
4 Ray KJ et al, for the Mycotic Ulcer Treatment Trial Group. *Am J Ophthalmol.* 2018;189:41-46.

Dr. Al-Mohtaseb is assistant professor of ophthalmology and associate director of the Residency Program at Baylor College of Medicine in Houston. *Relevant financial disclosures: None.*
Dr. Jeng is professor of ophthalmology and chair of the Department of Ophthalmology & Visual Sciences at the University of Maryland School of Medicine in Baltimore. *Relevant financial disclosures: None.*
Dr. Lietman is director of the Francis I. Proctor Foundation for Research in Ophthalmology and professor of ophthalmology, epidemiology, and biostatistics at UCSF. *Relevant financial disclosures: None.*
Dr. Rose-Nussbaumer is a cornea and external disease specialist and assistant professor of ophthalmology at UCSF. *Relevant financial disclosures: NEI: S.*
See the disclosure key, page 10. **For full disclosures,** find this article at aao.org/eyenet.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Position your practice for success

NEW Open to physicians and administrators

Ophthalmology Business Summit

March 23-24, 2019 | Chicago

Join us in addressing the urgent business challenges facing ophthalmic practices right now.

You'll acquire strategic insights and tactical tools that can be applied immediately and have a meaningful impact on your revenue and growth.

Seats are limited. Register today.
aao.org/business-summit

Early registration deadline is Dec. 6

Protecting Sight. Empowering Lives.®

Setting Meaningful Pressure Goals for Patients With Glaucoma

Elevated intraocular pressure (IOP) is a well-recognized risk factor for glaucoma, and efforts to lower IOP—often to a prespecified target—are a mainstay of glaucoma management. Yet whether and how to set a pressure goal and apply it as a therapeutic guide remains a source of contention among ophthalmologists.

Target IOP: Defined and Debated

In the Academy's 2015 *Preferred Practice Pattern* (*PPP*) for primary open-angle glaucoma (POAG), an expert panel defined target pressure as the upper limit of a range of IOPs in which "visual field loss is unlikely to significantly reduce a patient's health-related quality of life over his or her lifetime."[1]

Opinions. Target setting gives the practitioner a clear therapeutic goal, said L. Jay Katz, MD, of Wills Eye Hospital in Philadelphia. "It would be a mistake not to have a target pressure because lowering pressure is what we're doing with every therapy for glaucoma."

Even so, Kuldev Singh, MD, MPH, of Stanford University in California, cautioned that having a target IOP does not necessarily lead to better medical care. The natural history of glaucoma cannot be predicted prospectively and depends, in part, on factors that we don't fully understand.[2] He explained, "When we're setting a target IOP, we're trying to predict the pressure that will allow patients to see well for the rest of their lives, without knowing the patient's life span or the relationship between IOP and disease progression for that individual."

Ahmad A. Aref, MD, MBA, from the University of Illinois College of Medicine in Chicago, said that the concept of target setting can be valuable in practice, but only if the physician recognizes that "the target is not written in stone."

TRACKING PRESSURE. *New pressure monitoring devices, the Triggerfish Sensor (left) and HOME tonometer (right), allow for around-the-clock monitoring to help track peak pressures.*

Measuring IOP

When and how should IOP be measured? Dr. Katz noted that eye pressures vary during the day, and the highest pressures usually occur outside of office hours. During the night, pressures often peak.[3] "Ideally, you would ask the patient to be checked at different times of day and obtain a diurnal curve of the pressure," he said.

The reality, however, is that measurements are limited by practicality and logistics, said Dr. Aref. Even conscientious patients whose disease status is urgent may not come in for multiple IOP checks, especially if they have to go through all kinds of barriers to make it into the office for an eye pressure check, he said.

New technology. Dr. Katz noted that emerging technologies may soon make it easier to determine peak pressures at baseline and after treatment. The HOME tonometer (iCare) and the Triggerfish Sensor smart contact lens (Sensimed AG) have recently been approved for use in the United States and can generate many IOP-related measurements in a day, he said. In a recent study, ocular volume and elasticity–derived parameters obtained by a contact lens sensor for a 24-hour period offered a better explanation of glaucoma progression rates than did a series of traditional, in-office IOP measurements.[4]

Setting the Initial Target

Although there is no universally accepted formula for calculating a target pressure, much of the decision-making

BY JENNIFER S. GRIFFIN, MS, CONTRIBUTING WRITER, INTERVIEWING **AHMAD A. AREF, MD, MBA, L. JAY KATZ, MD,** AND **KULDEV SINGH, MD, MPH.**

is based on the peak IOP at baseline, said Dr. Katz.

Methods of target setting. Dr. Aref summarized three methods for setting a target IOP for a new glaucoma patient: 1) a percentage reduction from the baseline pressure, 2) a fixed number or range based on the disease stage, or 3) a formula that includes individual factors such as age, visual field loss, and baseline pressure. His preferred method is the percentage reduction from baseline. The 2015 *PPP* concurs that "a reasonable initial treatment in a POAG patient is to reduce IOP 20%-30% below baseline."[1] Well-known randomized controlled trials support this recommendation.[5-7]

Dr. Aref also considers factors like risk tolerance and life expectancy to help establish a safe target IOP. Dr. Katz added that family history can give important clues about how the glaucoma may progress.

Determining baseline IOP. Dr. Aref noted that he often sees referred patients who already have a diagnosis of glaucoma and are on treatment. In these cases, "I make every effort to determine the patient's unmedicated baseline IOP, either by contacting the physician who started the patient's treatment, or, if I think the patient's optic nerve can handle it, with a drug washout."

Assessing structure and function. To gauge glaucoma severity, Dr. Aref and his team use structural measures, such as stereoscopic optic disc examination and optical coherence tomography, as well as functional methods, such as automated visual field tests. "Based on these assessments, we can stage a patient's glaucoma as ocular hypertension or mild, moderate, or severe glaucoma." He added that some physicians then select a fixed target IOP based on disease stage, for example, 18 mm Hg for mild glaucoma, 15 mm Hg for moderate glaucoma, and 12 mm Hg for severe glaucoma. It is important to clarify that staging based on structural and functional measures for the purpose of target pressure determination does not always correspond with current ICD-10 glaucoma staging definitions, which only take into account functional data, he said.

The Safety Factor

The concept of target IOP does not address the safety of the therapies required to reach a predetermined pressure level, Dr. Singh said. "You have to ask yourself, 'What are the risks of getting to that IOP goal, and are they worth taking?'" This is especially true when the patient has mild glaucoma or when disease progression has not been observed, he said.

Incremental risk. You should never treat a patient to the point beyond which the expected harm of the next therapeutic step would be greater than the expected benefit, given what you know about that patient's disease at that time, Dr. Singh said. This thinking lies at the foundation of starting with relatively safe treatments, like eyedrops, before advancing to riskier surgical options.

He added that this dynamic approach, based on risks and benefits of therapy, is more abstract than setting an IOP target and treating until you reach it. Yet he emphasized that the dynamic approach is "unquestionably the one used by most experienced practitioners."

Advanced disease. Dr. Singh considers the concept of target IOP to be "hypothetically useful in very severe glaucoma," in which risks of glaucomatous visual loss considerably outweigh risks of treatment. Dr. Katz summed it up as "Generally, the more severe the disease, the more aggressive we are with trying to reach a low target pressure."

Changing the Goal

"The target IOP is fluid, and we may decide that the target set initially was overly conservative or aggressive," said Dr. Katz. He added, "Each of the patient's eyes may have a different pressure goal, and the target can change over the course of the disease."

Dr. Singh said that with a target pressure approach, ophthalmologists need to be prepared to change the IOP goal at every visit, based on available clinical findings and the safety profile of the remaining therapeutic options.

The 2015 *PPP* states that physicians should adjust the initial target pressure as indicated by disease course and severity,[1] but Dr. Singh noted that this recommendation omits mention of the side effects and risks of treatment. He stressed that these factors "should be at the forefront of your mind, especially because glaucoma does not always lead to visual impairment."

Realistic Expectations

Although Dr. Singh does not dispute that lowering IOP can slow glaucoma progression, he said, "the notion that achieving a target IOP will completely arrest the disease is problematic." Instead, he advocates thinking in terms of rates of change. "Glaucoma is always progressing because of the aging component of ganglion cell loss layered onto the disease component." Accordingly, he said that practitioners should take time to inform patients that glaucoma management is complex, the disease course can be unpredictable, and treatment adherence is strongly recommended, but it will not guarantee a good outcome.

Dr. Singh and his colleagues have identified several obstacles to meaningful IOP targeting: suboptimal measuring tools, the uncertainty of a patient's life span, unforeseeable complications of therapy, and the likelihood that the patient's priorities or risk tolerance may shift during the course of the disease.[8]

The Bigger Picture

"The main goal is preserving the patient's vision," said Dr. Aref. "The status of the patient's optic nerve and visual field are the metrics that I'm actually following, but they don't change rapidly. The IOP is a surrogate for those more important measures."

Dr. Singh added, "We must make decisions within the limits of resolution of our diagnostic tools."[8] He explained that specifying and achieving a target IOP are not necessarily indicative of treatment success, disease stabilization, or an eliminated risk of blindness. "Ultimately, glaucoma care is not about the IOP or even about saving every ganglion cell and optic nerve fiber. Rather, it is about optimizing the patient's health."

Dr. Aref reiterated that the target pressure is a starting point. "Even in

two hypothetical patients with the same baseline pressures, same targets, and same visual fields, you may end up treating each very differently."

Dr. Katz added, "There is considerable science behind what we do in managing glaucoma, but there is art to it as well. You must weigh a lot of factors specific to the patient."

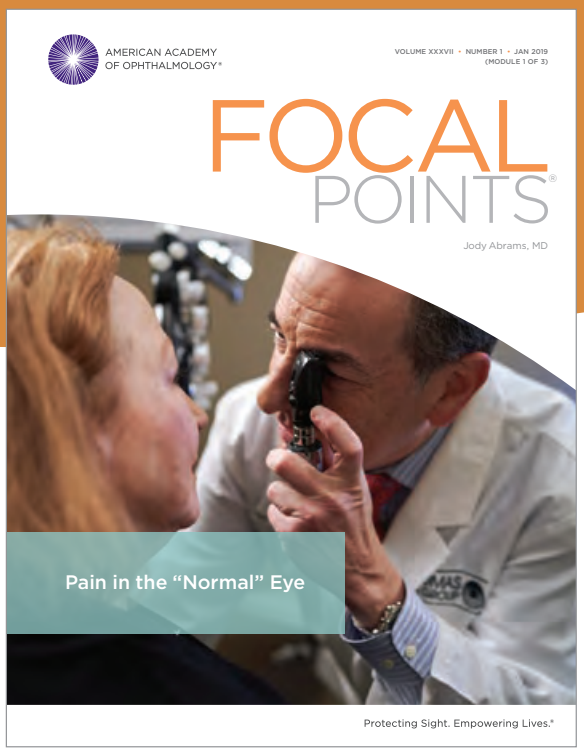
1 Prum BE Jr et al. *Ophthalmology*. 2016;123(1): P41-P111.
2 Singh K, Shrivastava A. *Surv Ophthalmol*. 2008; 53(6):S33-S38.
3 Liu HK et al. *Invest Ophthalmol Vis Sci*. 2003; 44:1586-1590.
4 De Moraes CG et al. *Ophthalmology*. 2016; 123(4):744-753.
5 Heijl A et al for the Early Manifest Glaucoma Trial Group. *Arch Ophthalmol*. 2002;120(10): 1268-1279.
6 Anderson DR et al for the Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol*. 1998;126(4):487-497.
7 Kass MA et al for the Ocular Hypertension Treatment Study. *Arch Ophthalmol*. 2002; 120(6): 701-713.
8 Singh K et al. *Ophthalmology*. 2000;107(4):629-630.

Dr. Aref is director of the residency program and associate professor of ophthalmology, University of Illinois College of Medicine, Chicago. *Relevant financial disclosures: None.*
Dr. Katz is director emeritus of the Glaucoma Service, Wills Eye Hospital, and is professor of ophthalmology, Thomas Jefferson University, both in Philadelphia. *Relevant financial disclosures: None.*
Dr. Singh is professor of ophthalmology, Stanford University Medical Center, Stanford, Calif. *Relevant financial disclosures: None.*
For full disclosures, see this article at aao.org/eyenet.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Advance Your Patient Care with Practice-Ready Research

Focal Points® curates the most crucial advances so you can focus on findings that make a significant difference for your patients.



Each issue features quick tips to help you integrate tested research into your practice. Listen to the new audio version for info on the go.

Don't fall behind the curve. Subscribe at **aao.org/focalpoints**.

Rhegmatogenous Retinal Detachment: Management, Part 2

Last month, Ophthalmic Pearls discussed risk factors, features, and examination of rhegmatogenous retinal detachments (RRD). This month, the authors continue with a discussion of RRD management.

After Dx: How to Proceed

RRDs with superior breaks that threaten the macula require urgent vitreoretinal intervention. While awaiting definitive management, patients should maintain a posture that prevents the subretinal fluid from detaching the macula.

Definitive management of RRD includes barrier laser retinopexy in select situations, pneumatic retinopexy, primary scleral buckle, primary pars plana vitrectomy (PPV) with intraocular tamponade or combined scleral buckle and vitrectomy.

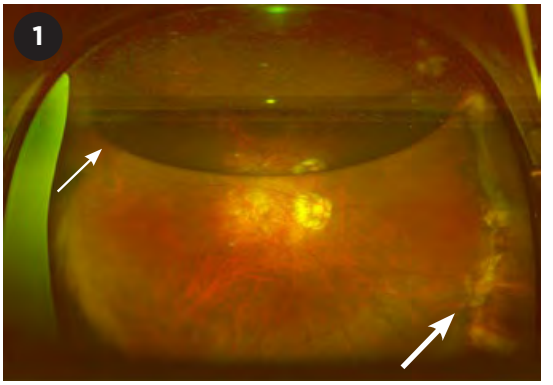
Barrier laser retinopexy. This procedure is indicated for localized detachments such as subclinical retinal detachment. This is usually performed with the patient under topical anesthesia. Patients must be forewarned that, despite this treatment, the RRD may progress and require additional intervention, including surgery.

Pneumatic retinopexy. Pneumatic retinopexy is indicated for specific RRD cases, including those with break(s) confined to the superior 8 clock hours, with all breaks being confined within 2 clock hours. Contraindications include large (giant) retinal tears, proliferative vitreoretinopathy (PVR), advanced glaucoma, poor compliance with head posturing, individuals who need to travel by air, and, in some cases, pseudophakia.

The procedure, which is performed with the patient under regional anesthesia, entails transconjunctival intravitreal injection of an expansile gas bubble, plus retinopexy to the retinal breaks. In general, retinopexy is done using cryotherapy or laser photocoagulation. Transconjunctival cryopexy usually is performed before gas injection, during a single outpatient visit. For laser retinopexy, gas injection is performed initially, followed by laser photocoagulation several days later. The expansile intraocular gases include 100% sulfur hexafluoride (SF_6, 0.6 mL), perfluoroethane (C_2F_6, 0.4 mL), and perfluoropropane (C_3F_8, 0.3 mL).

Reattachment can be achieved with a single pneumatic retinopexy procedure in 80% of cases and with ≥1 procedure in 98%.[1]

Although pneumatic retinopexy is minimally invasive, the risk of new or missed retinal breaks is greater with this procedure than with more invasive surgery such as vitrectomy or scleral buckle.[2] Other possible complications include gas migration into the subretinal space, central retinal artery occlusion from elevated IOP, vitreous incarceration at the wound, accelerated cataract formation, and endophthalmitis.



AFTER COMBINATION SURGERY. *Ultra-widefield fundus photograph of an eye that underwent scleral buckle and PPV with gas. The photograph was obtained several weeks postoperatively. A partially resorbed gas bubble is visible (small arrow), and the indent from the buckle can be seen supporting the peripheral retina (large arrow).*

Scleral buckle and pars plana vitrectomy. All breaks must be located, then treated with cryotherapy or laser retinopexy. Vitreoretinal traction must be relieved by either scleral buckling or vitrectomy. In most cases, the subretinal fluid is drained internally (via the retinal hole during vitrectomy) or externally (by scleral cut-down in primary scleral buckle surgery), if needed.

Scleral buckle surgery. This extraocular procedure should be considered for young, phakic patients with tear(s)

BY **NATHALIE PEI YU CHIAM, MD, DANIEL SHU WEI TING, MD, PHD, LEE SHU YEN, FRCS(ED),** AND **CHONG LYE ANG, FRCOPHTH.** EDITED BY SHARON FEKRAT, MD, AND INGRID U. SCOTT, MD, MPH.

The Ocular Imaging Department, Singapore National Eye Centre

anterior to the equator. It is not suitable for patients with a giant retinal tear or PVR.

Transscleral cryotherapy is performed around the retinal break, and the external scleral indentation from the buckle helps to support the break. The buckle-induced indentation aids in adhesion between the neurosensory retina and the retinal pigment epithelium, while relieving vitreous traction on the retina.[3] Several types of scleral buckling material are available, including encirclage and segmental and radial buckles. The procedure is usually performed in the operating room while the patient is under regional anesthesia or, rarely, general anesthesia.

Surgical steps are as follows:

- 360-degree conjunctival peritomy
- Slinging recti muscles
- Localizing the break with binocular indirect ophthalmoscopy (BIO)
- Cryotherapy with or without external drainage of subretinal fluid
- Inserting the segmental and/or encircling scleral buckle
- Suturing and tightening of the buckle
- Checking of central retinal artery perfusion to determine need for anterior chamber paracentesis
- Antibiotic wash around the buckle
- Closing the conjunctiva
- Subconjunctival antibiotic and steroid injections

Intraoperative complications include scleral perforation and recti muscle trauma/slip. In cases requiring subretinal fluid drainage, the surgeon must be aware of risk for suprachoroidal hemorrhage, hypotony, and retinal incarceration at the drainage site. Postoperative complications include PVR formation, re-detachment, buckle migration/extrusion, buckle-related infections, refractive changes, ocular motility disorders, anterior segment ischemia, and glaucoma (from vortex vein or ciliary body compression).

Among suitable cases, reattachment can be achieved with a single primary scleral buckle procedure in 80% to 90%.[4]

Pars plana vitrectomy. PPV may be indicated for posterior retinal break, multiple breaks in different meridians, giant retinal tear, concurrent PVR, and dense vitreous hemorrhage obscuring the retinal break(s). PPV is performed in the operating room while the patient is under regional anesthesia or, rarely, general anesthesia.

Steps include:

- Creating three sclerostomy ports (for the infusion cannula, illumination probe, and vitrectomy handpiece)
- Core vitrectomy, shaving the vitreous base, and relieving any traction over the retinal break
- Using perfluorocarbon liquid to flatten the retina and displace the subretinal fluid via the original retinal break (optional step, depending on surgeon preference)
- Retinopexy around retinal breaks; laser is often used
- Fluid-air exchange
- Injecting vitreous substitute such as isoexpansive gas or silicone oil

Nonexpansile intraocular gas tamponade, such as SF_6 20%, C_2F_6 15%, or C_3F_8 15%, will usually last two weeks, three weeks, and eight weeks (respectively) due to different rates of resorption. Patients should be advised about the postoperative posturing necessary to allow the buoyant vitreous substitute to tamponade the break. This posturing is maintained until most of the gas bubble has been resorbed.

If silicone oil tamponade is used, it is typically removed three to six months after surgery; in some eyes, it is retained indefinitely.

The success rate of PPV for RRD ranges from 64% to 96%, depending on the complexity of the case.[5]

Intraoperative complications include trauma to intraocular structures (e.g., iatrogenic retinal breaks or iatrogenic cataracts) and vitreous/retina incarceration at sclerotomy wounds. Postoperative complications may include endophthalmitis, sympathetic ophthalmia, glaucoma, and cataract.

Combined scleral buckle and pars plana vitrectomy. This combination is sometimes needed for simple RRD (Fig. 1). Although most comparative studies of scleral buckle, PPV, and the combination procedure showed no significant differences in success rates for single-session surgery, a few have demonstrated that PPV alone is superior to scleral buckle alone for primary RRD.[5] In a retrospective study at Singapore National Eye Centre, patients who received the combination procedure had better anatomic success rates than those who underwent PPV alone (90% vs. 80%, $p < .001$).[6]

In complicated RRD cases, combining scleral buckle and PPV can improve visualization of breaks during PPV and provide better support of the peripheral retina.

Timing of Intervention

The urgency to repair RRD depends on the status of the macula and other patient-specific characteristics. Even if the macula is on (fovea spared), urgent intervention may be necessary. When the fovea is already detached (macula-off), reattaching the retina may be less urgent. Some experts suggest that the number of days of foveal detachment may indicate the urgency of surgery. Thus, if the fovea has been detached for two days, surgery should be performed within two days.[7]

In a study of patients with macula-off retinal detachment, those who underwent surgery within three days of developing central vision loss had better visual outcomes postoperatively.[8] However, the visual outcomes for cases in which surgical repair was delayed for 10 days did not differ significantly from outcomes for cases not surgically repaired until a month following the loss of central vision.[8]

Conclusion

The management of RRD requires a detailed assessment to ensure identification of all breaks. This facilitates the planning and execution of surgical intervention. Surgical treatment entails locating and sealing all breaks as well as relieving vitreous traction. Prompt intervention may produce better visual outcomes. Care should be taken to select the most appropriate procedure or procedures, with consideration given to the timing of intervention.

1 Hilton GF, Tornambe PE. *Retina.* 1991;11(3):285-294.

2 Chan CK et al. *Surv Ophthalmol.* 2008;53(5):

443-478.
3 Sullivan P. Techniques of scleral buckle. *Ryan's Retina*, Vol 3. 6th ed. Philadelphia: Elsevier; 2017: 1889-1915.
4 Thelen U et al. *Acta Ophthalmol.* 2012;90(5): 481-486.
5 Young HY et al. Primary vitrectomy in rhegmatogenous retinal detachment. *Ryan's Retina,* Vol 3. 6th ed. Philadelphia: Elsevier; 2017:1933-1942.
6 Wong CW et al. *Retina.* 2014;34(4):684-692.
7 Hassan TS et al. *Ophthalmology.* 2002;109(1): 146-152.
8 Frings A et al. *Br J Ophthalmol.* 2016;100(11): 1466-1469.

Dr. Chiam is an ophthalmology resident at Singapore National Eye Centre. **Dr. Ting** is the surgical retinal fellow at the Singapore National Eye Centre and an assistant professor at Duke-National University Singapore (Duke-NUS) Medical School. **Dr. Lee** is the senior consultant, deputy head of the Surgical Retinal Department of Singapore National Eye Centre, and an adjunct associate professor at Duke-NUS. **Dr. Ang** is a senior consultant at the Surgical Retinal Department of Singapore National Eye Centre and a clinical professor at Duke-NUS. *Financial disclosures: None.*

Acknowledgment: We thank the Ocular Imaging Department, Singapore National Eye Centre, for providing the retinal photographs in Parts 1 and 2 of this series.

WRITE A PEARLS ARTICLE

Interested in sharing with your colleagues an overview of a specific disease entity based on the latest evidence?

Pearls articles typically offer step-by-step summaries of etiology, diagnosis, treatment, and follow-up.

To get started, you only need:

- a great topic
- a faculty advisor to review your manuscript and add his/her pearls from clinical experience
- a copy of the Writers Guidelines for Ophthalmic Pearls. Find them at aao.org/eyenet/write-for-us.

Are you a resident? A resident article published in Ophthalmic Pearls will satisfy the RRC requirements for resident scholarly activity.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

I believe in high surgical standards. I protect sight.

I support the Surgical Scope Fund.

"Cataract surgery is a beautiful, elegant procedure. I've spent countless hours studying, practicing, and traveling to become the best cataract surgeon I can be. It's frightening to think that this demanding procedure or any other eye surgery could be performed by anyone other than a highly-trained ophthalmic surgeon. We each took an oath to protect our patients. That's why I contribute to the Surgical Scope Fund and that's why I'm urging you to do the same."

ROBERT H. OSHER, MD
Professor of Ophthalmology, College of Medicine, University of Cincinnati; Medical Director Emeritus of Cincinnati Eye Institute

When high surgical standards are threatened nationwide, the Academy's Surgical Scope Fund can deliver resources, expertise and winning strategies for protecting patient safety and preserving surgery by surgeons.

Make your confidential Surgical Scope Fund contribution today at aao.org/ssf.

The Curious Case of Cysts and Sight

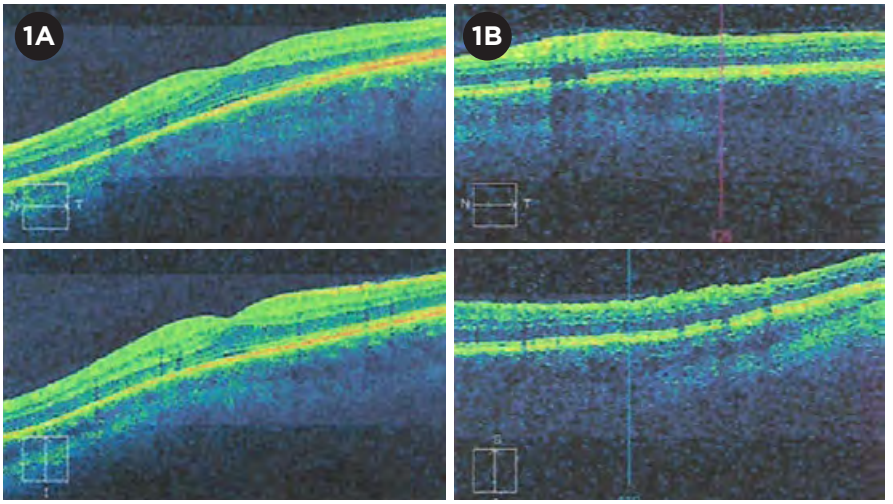
Jeffrey Jones,* a previously healthy 29-year-old man, presented with a 10-month history of progressive visual acuity decrease in his left eye, which started when his vision became hazy following an episode of presumed ocular migraine. Worried about the continuing decline in his vision, he came to us for help.

We Get a Look

When we saw him, Mr. Jones stated that objects lacked definition, but he said that he was not aware of any visual field loss. His previous medical history was unremarkable.

Upon examination, uncorrected visual acuity (VA) was 20/20 in the right eye and 20/50 in the left eye. Pupils were equal, round, and reactive to light, without a relative afferent pupillary defect. Anterior segment examination was normal bilaterally. Intraocular pressure (IOP) was 12 mm Hg in his right and left eyes. Confrontation visual fields were full to counting fingers in both eyes. Ocular movements were full and painless. External examination showed normal eyelids and eyelashes with hypoglobus of the left eye.

Funduscopic examination showed a normal optic nerve with normal cup-to-disc ratio bilaterally. The macula was normal in the right eye. In the left eye, we observed faint striae in the macular region, extending superiorly to the midperiphery. Blood vessels in both eyes appeared normal. Extended peripheral exam of the retina was normal in both eyes.



OCT. *(1A) OCT image of the central macula of the right eye shows normal foveal contour. (1B) Retinal striae are visible in superior macula of the left eye.*

The classic mnemonic for recalling etiologies of chorioretinal striae is THIN RPE: T, tumor; H, hypotony; I, inflammation or idiopathic; N, neovascularization; R, retrobulbar mass; P, papilledema; E, extraocular hardware. With this list in mind—as well as the patient's age, normal IOP, exam findings, and absence of prior ocular surgery—we developed a differential diagnosis that included choroidal tumor, posterior ocular inflammation, retrobulbar mass, and idiopathic etiology.

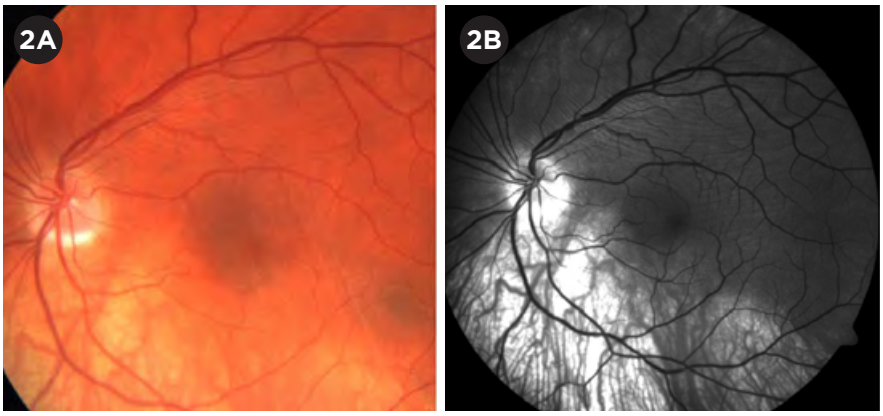
Further Investigations

Given the patient's blurred vision and striae, we ordered additional testing. Optical coherence tomography (OCT) images of the left eye supported our earlier funduscopic impression of macular striae superiorly (Fig. 1B). B-scan ultrasonography of the left eye showed an extraocular hyperreflective plaque in the superior temporal midperiphery. Color fundus and red-free fundus photographs of the left eye revealed retinal striae involving the central and superior macula (Fig. 2).

Based on these findings, we requested a computed tomography (CT) scan of the head and orbit (Fig. 3). It showed a hypodense expansive mass, measuring 1.6 × 2.9 cm, within the zygomatic process of the left frontal bone. This mass eroded through the orbital roof and extended into the orbit, causing inferior

BY **EMILEE DAILEY, MD, SAMUEL THOMSEN, MD, GEETHA DAVIS, MD, RYAN DAVIS, MD, MATTHEW HIRABAYASHI,** AND **VIKRAM PONNUSAMY.** EDITED BY STEVEN J. GEDDE, MD

Mason Eye Institute, University of Missouri Hospital, Columbia



PHOTOS. *(2A) Color fundus photograph and (2B) red-free fundus photograph; both images reveal retinal striae involving the central and superior macula.*

displacement and deformation of the left globe. Magnetic resonance imaging (MRI) showed a well-defined lesion that appeared hyperintense on both T1- and T2-weighted images, without significant enhancement (Figs. 4-6).

Our differential diagnosis at that time included cholesterol granuloma, mucocele, cholesteatoma, and epidermoid cyst. After further discussion between ophthalmology, otolaryngology, and neurosurgery, surgical removal was determined to be the best treatment option. Mr. Jones underwent tumor excision with orbital reconstruction. The pathology report identified the tumor as a cholesterol granuloma. At postoperative day 1 the patient felt his vision was still blurry but denied worsening. Two weeks after surgery, the patient was seen in the neurosurgery clinic and subjectively felt that his vision had improved and that he was able to read better.

Follow-up Visits

Five months after surgery, Mr. Jones returned to our ophthalmology clinic. He reported a "catching" sensation when he woke up in the morning and difficulty moving his left eye down. Uncorrected VA was 20/15 in the right eye and 20/50 in the left eye. We saw no abnormalities on exam except for mild retinal striae along the superior arcade in the left eye, consistent with the location of the excised tumor that had been indenting the globe. A CT of the head and face was ordered; it showed that the orbital roof fixation plate placed at the time of surgery was protruding into the orbit and impinging on the globe (Fig. 7). Surgery was performed and the orbital plate from the previous surgery was found to be impinging on the superior rectus and superior oblique muscles without damage to the globe. The impinging portion of the plate was removed, leaving a small defect in the roof of the orbit that was considered insignificant.

Mr. Jones was seen in the ophthalmology clinic two days postoperatively. He no longer felt the "catching" sensation and was able to move his left eye without difficulty. On dilated fundus exam, mild retinal striae were still present, and VA of the left eye was 20/50. The patient was scheduled to return in six months but was lost to follow-up.

Four years have passed since the revision. We contacted him recently, and he reported a VA of 20/30 in his left eye during a recent eye exam.

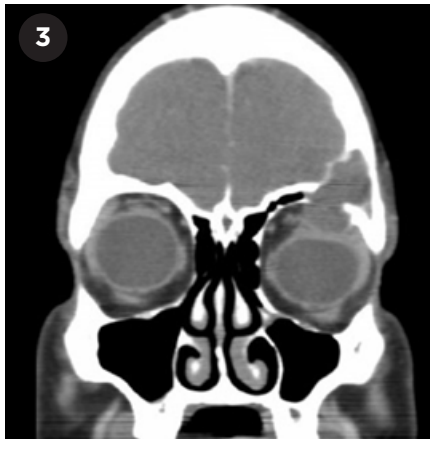
Discussion

Cholesterol granuloma is a rare diagnosis that has been reported in several anatomic locations. The most common of these sites are the middle ear, mastoid antrum, and petrous apex.[1] Less frequent locations include the frontal bone, zygoma, paranasal sinuses, breast, peritoneum, testes, and lung. When a cholesterol granuloma forms in the orbital region, it occurs most often within the lacrimal region of the frontal bone. It is unknown why this region is most commonly affected.

Pathogenesis. The etiology of orbital cholesterol granulomas is currently unknown, but several hypotheses have been proposed. The most-accepted hypothesis is that an unabsorbed hematoma from an episode of mucosal bleeding in the frontal sinus leads to deposition of cholesterol crystals, causing a foreign body chronic inflammatory response.[2] Although the inciting event is unclear, trauma could be a trigger.

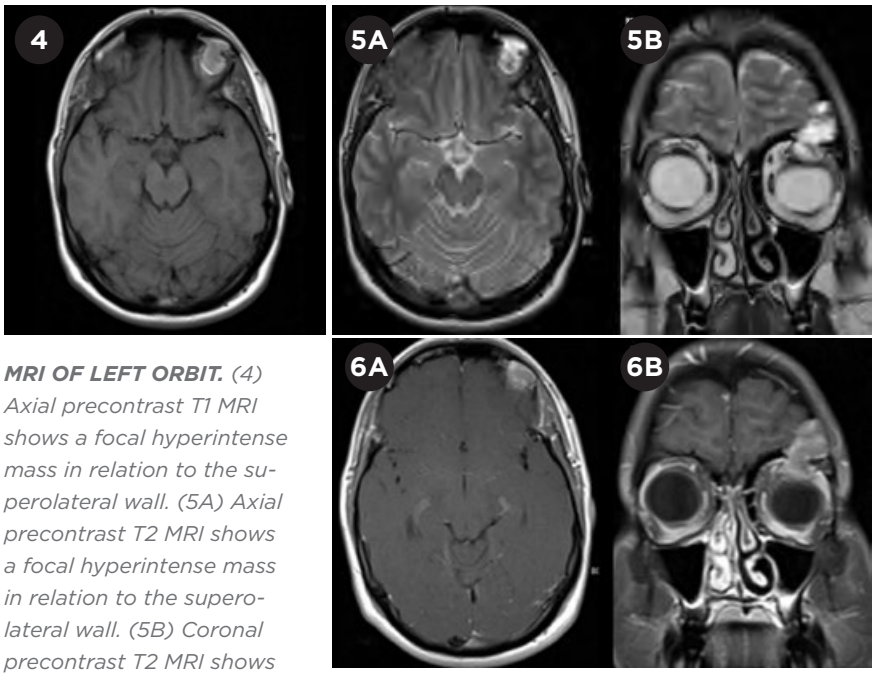
Imaging. Both CT and MRI are helpful in diagnosing a cholesterol granuloma. A noncalcifying lesion that is isodense with brain, round with a smooth outline, and located in the superolateral bony orbit is typically seen on CT. On MRI, cholesterol granulomas show bright signal intensity on both T1- and T2-weighted images due to the presence of hemoglobin breakdown products around the cholesterol crystals.[3] Both of these findings were used to describe the mass in our case, and even before surgical removal, cholesterol granuloma was considered to be the most likely diagnosis.

Treatment/histology. The definitive treatment for a cholesterol granuloma is drainage and total removal of the granulomatous tissue. Although recurrence is rare, curettage of any residual granulomatous material adhering to the bone and periosteum is necessary to further reduce the chance of recurrence.[4] Once removed, the lesion should be sent to pathology for a histologic diagnosis, which classically shows foreign body giant cells surrounding cholesterol clefts, chronic inflammatory



PREOP SURGERY 1. *Coronal CT shows left frontal bone mass extending into the orbit with displacement and deformation of the left globe.*

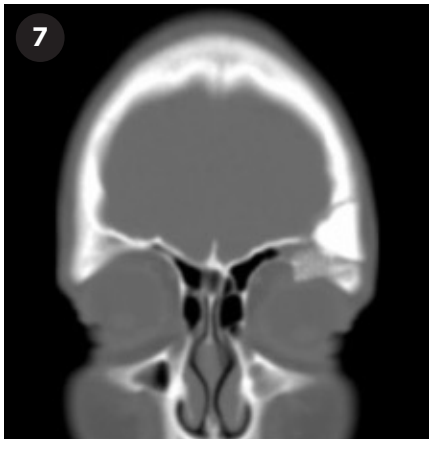
Mason Eye Institute, University of Missouri Hospital, Columbia



MRI OF LEFT ORBIT. *(4) Axial precontrast T1 MRI shows a focal hyperintense mass in relation to the superolateral wall. (5A) Axial precontrast T2 MRI shows a focal hyperintense mass in relation to the superolateral wall. (5B) Coronal precontrast T2 MRI shows a hyperintense mass in relation to the superolateral wall. (6A) Axial postcontrast T1 MRI shows a focal hyperintense, nonenhancing mass in relation to the superolateral wall. (6B) Coronal postcontrast T1 MRI shows a focal hyperintense, nonenhancing mass in relation to the superolateral wall.*

infiltrate, and hemorrhagic products—all of which are characteristics of a cholesterol granuloma.

Patient's course. When Mr. Jones was seen in our ophthalmology clinic after his final surgery, we assumed that his vision had not improved because of the continued striae in the presence of the implant. When we communicated with him four years later, he stated that the VA in his left eye was 20/30. Based on that information, we speculated that the striae resolved after revision surgery, resulting in an improvement in vision. However, it remains unclear why his vision did not improve to 20/20 following revision. Unfortunately, we have no records of the patient's baseline VA before presentation, which might have helped explain his outcome.



PREOP SURGERY 2. *Coronal CT shows the fixation plate extending into the bony orbit and impinging on the superior surface of the left globe.*

* Patient name is fictitious.

1 Royer MC, Pensak ML. *Curr Opin Otolaryngol Head Neck Surg.* 2007;15(5):319-322.
2 Selva D et al. *Clin Exp Ophthalmol.* 2003;31(1):78-82.
3 Dubrulle F et al. *Radiology.* 2006;238(2):604-610.
4 Hoa M et al. *J Laryngol Otol.* 2013;127(4):339-348.

Dr. Dailey is a PGY1 resident who will begin ophthalmology residency at the University of Alabama at Birmingham, Callahan Eye Hospital, in July 2019. **Dr. Thomsen** is a PGY4 ophthalmology resident, and **Dr. G. Davis** is the residency program director and an assistant professor of clinical ophthalmology; both are at the Mason Eye Institute at the University of Missouri Hospital, Columbia. **Dr. R. Davis** is an assistant professor of clinical radiology at the University of Missouri Hospital in Columbia. **Mr. Hirabayashi** and **Mr. Ponnusamy** are medical students at the University of Missouri School of Medicine in Columbia. *Financial disclosures: None.*


Tools

VR Meets Medical Education

Why "see one, do one, teach one" will never be the same.

By Linda Roach, Contributing Writer

Is virtual reality (VR) the future of ophthalmic medical education? It may well be. VR offers residents a risk-free way to learn diagnostic and surgical skills—and it does so in a compelling, immersive, 3-D manner. VR's potential is also expected to extend well beyond residency to midcareer surgeons who want to refine their skills or learn new procedures.

Here's a look at two VR platforms developed specifically for ophthalmic education.

EyeSim: Student Immersion

For the past six years, Anuradha Khanna, MD, has been using VR simulation tools to augment traditional methods of teaching medical students and residents about ophthalmology.

"Virtual reality provides us with a medium in which we can simulate the micro and the abstract, and it allows the students the opportunity to practice and practice in a safe environment until they achieve mastery," said Dr. Khanna, at Loyola University in Chicago.

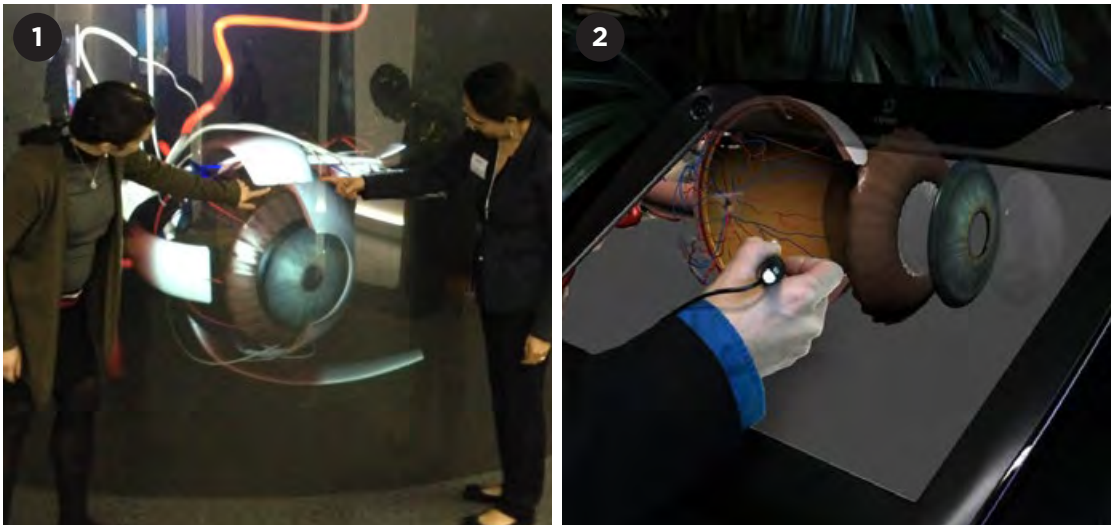
Stereo classroom. Dr. Khanna developed the ophthalmic VR software that Loyola uses, called EyeSim (A Nu Reality). Several other medical schools and ophthalmology training programs around the country have adopted it.

Instead of wearing VR headsets, the teacher and students wear special glasses that enable them to see images displayed on a classroom screen or mobile device in three dimensions. "In a stereo classroom, we all wear 3-D glasses, and the content is interactive," Dr. Khanna said. "If I'm taking them through the blood vessels in the eye, or through the visual pathways starting from the retina all the way to the brain, I can stop and change the angle and rotate the anatomy [and] zoom in and out." The result is essentially a virtual dissection, she said.

Each student also can view these same anatomical images—or conduct a simulated eye exam—on a large, mobile holographic display (the "Ibench") in a skills transfer lab, she said. Motion sensors in the 3-D glasses enable the student to rotate and zoom the images via head movement. "Or they can study independently on their smartphones or their smart tablets," she said.

"Wow!" factor. The strategy of delivering information via the triad of a stereo classroom, a hands-on simulation skills lab, and a discussion with feedback has proved to be an effective one, Dr. Khanna said. "We are not providing information for the students, we are actually leading them toward conceptual clarity and refining their examination skills. I've witnessed, many times, the 'Wow!' factor that happens when they understand the correlation between the clinical presentation and the anatomical pathology."

Anuradha Khanna, MD



EYESIM. *Images can be seen on 3-D classroom screens (1) and a large, mobile holographic display (2).*

Dr. Khanna added, "You don't have to motivate them to pick up a book or pay attention. Nobody's on their cell phone texting or pretending to take notes during these sessions. They are immersed in the training," she said. "And because, generally, we have limited time, I really have to almost peel them away from these simulators to move along to the next station. They're enjoying it."

Potential drawbacks. Despite her enthusiasm for EyeSim, Dr. Khanna said that there are both human and economic barriers to bringing a VR focus to ophthalmic education. "Faculty buy-in is slow, because faculty members commonly lack experience with VR-based teaching tools," she said.

The technological and development costs are significant, she said. For instance, a comprehensive EyeSim system includes multiple Ibench holographic displays, stereo classroom screens, and the VR software itself. "It also is costly and time-consuming for companies to develop high-quality VR educational content. What we have available thus far is limited," she said.

Eyesi: Minimizing Risk to Patients

The most widely used device for performing virtual ophthalmic surgery is Eyesi Surgical (VRmagic), a system designed to train novices in cataract and vitreoretinal surgery.

More than 300 Eyesi Surgical simulators are in use around the world, with more than 100 of them in the United States. VRmagic also sells separate simulators that allow users to practice direct and indirect ophthalmoscopy. A new device, Eyesi Slitlamp, was unveiled at AAO 2018 in Chicago and is expected to be commercially available this year.

In Eyesi's cataract surgery version, the student looks through what appears to be a surgical microscope and manipulates handpieces to move attached instruments around "inside" the 3-D virtual anterior chamber seen in the oculars. In reality, the instruments are moving about in a hollow model of a reclining head. The system automatically generates a numerical assessment of how the student did on each step of the procedure, on a scale of 0-100; students and teachers can use the figures to track improvement over time.

Surgical training begins here. R. Michael Siatkowski, MD, at the Dean McGee Eye Institute in Oklahoma City, said ophthalmology residents at McGee are required to complete the Eyesi cataract surgery modules before proceeding to live surgery. "This has really revolutionized surgical education for residents, as opposed to the old method of 'see one, do one, teach one,'" Dr. Siatkowski said.

"We have anecdotally seen evidence that our residents are much more prepared to perform cataract surgery as a result of having completed these VR-based techniques. It allows the residents to begin to learn at a higher level in more complex situations when they're doing real surgery," he said. "And I think that most program directors with an Eyesi simulator would agree that it results in better patient care as well."

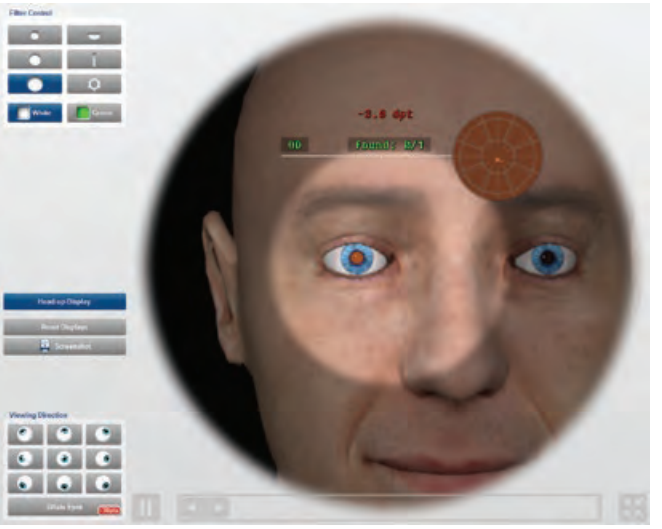
Risk-free. Andrew T. Melson, MD, a Dean McGee neuro-ophthalmology fellow who was chief resident there last year, said he was grateful that, during his first year of residency, he could learn to navigate the intraocular landscape in a virtual setting where the consequences were also virtual.

EyeSim

"I've spent probably the better part of 50 to 100 hours on a virtual reality surgical simulator, and I can attest to the fact that it has made me a better, more confident beginning surgeon," Dr. Melson said. "In a field where one wrong move during surgery can lead to blindness, the use of this type of technology to develop skills in a realistic environment shouldn't be underappreciated," he added.

Paradigm shift. The Eyesi training module for making a capsulorrhexis is particularly well-designed and helpful to students, Dr. Melson said.

"I've heard from several attendings that historically the capsulorrhexis was one of the most difficult parts of the surgery to teach—the step that they would save for later down the road, once the resident was well-versed in intraocular surgery," he said. "But with Eyesi training, it's oftentimes one of the easiest and most comfortable aspects of the procedure for residents. I've heard several attendings who have been very impressed with how quickly people become proficient at that step. That's been a huge paradigm shift."



EYESI. *Some residency programs require residents to complete the Eyesi cataract surgery modules before proceeding to live surgery.*

A recruiting tool? Most medical students have little or no exposure to ophthalmology in their regular curriculum, Dr. Siatkowski said. But they react enthusiastically when, as happens at Dean McGee, they are given the opportunity to do tasks or perform virtual eye surgery with the Eyesi, Dr. Melson said. "I think it actually serves pretty well as a recruitment tool," he said.

Disadvantages. The drawbacks of Eyesi lie chiefly in what is missing from the simulator and in its cost, Dr. Siatkowski said.

The tactile/proprioceptive feedback, though impressive, is still not identical to in vivo surgery, so users have an incomplete experience of what it feels like to, for instance, make a clear-corneal incision, deal with various degrees of tissue elasticity, or manipulate a lens, he said.

The device is expensive: about $170,000 for the cataract surgery version, and an additional $80,000 with vitreoretinal capabilities added.

"We still have further to go to make it more realistic and real-world. And, eventually, the cost has got to come down to make these more accessible to learners worldwide," Dr. Siatkowski said. "When those things happen, then the tool will also become useful for helping the established surgeon learn new techniques, as well as for measuring and assuring continued surgical competence among physicians who have completed training."

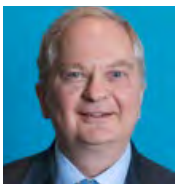
EXTRA **MORE ONLINE.** For video highlights of the EyeSim platform, see this article at aao.org/eyenet.

MEET THE EXPERTS

Anuradha Khanna, MD Professor of ophthalmology and vice chair of education at Loyola University's Department of Ophthalmology in Chicago. *Financial disclosures: A Nu Reality: O; EON Reality: C.*

Andrew T. Melson, MD Neuro-ophthalmology fellow at the Dean McGee Eye Institute in Oklahoma City. *Financial disclosures: None.*

R. Michael Siatkowski, MD David W. Parke II, MD, Professor of Ophthalmology, David Ross



Boyd Professor, vice chair for Academic Affairs, and director of the Residency Program at the Dean McGee Eye Institute in Oklahoma City. *Financial disclosures: None.*

See the disclosure key, page 10.

VRmagic

Best Practices for Coding: Six Do's and Don'ts

In the evolving world of ophthalmology, the correct way to go about doing things can change—and this is as true for coding as it is in the exam lane or the operating room. But if your practice observes these 6 best practices, your coding should remain tip-top.

1. Don't use a colleague's NPI. When new physicians are awaiting credentialing, there is a misconception that they can see patients under another physician's National Provider Identifier (NPI), provided that the physician who is already credentialed signs off on the charts. Not true, as this cautionary example shows: A new physician, Dr. D. Howser,* is using the NPI of his seasoned colleague, Dr. J. Kildare.* The apparent increase in Dr. Kildare's utilization of services put him on auditors' radar. When the documentation revealed that the exam and other services were not performed by Dr. Kildare, the payer recouped payment for the exams and tests, added a penalty, and began auditing him every 3-6 months.

2. Do keep the physician's signature secure. You will run into trouble if anybody other than the physician signs the physician's name on letters, chart notes, operating room progress notes, etc. When auditors reviewed Dr. Kildare's chart notes, for example, they turned the documentation over to the CMS fraud and abuse unit after noticing that he had two distinct signatures. (A circulating nurse had been signing Dr. Kildare's name on progress reports.)

3. Don't "correct" coding for an encounter without getting the physician's input. Dr. Kildare was being audited on E&M code 99214 for high volume. This surprised him, as he only uses Eye visit codes. It turned out that the biller, without consulting Dr. Kildare, had changed all 92014s to 99214s. Unfortunately, the chart note was not set up to capture the additional documentation that would be required to support that E&M code (i.e., the review of systems; the past, family, and social history; and at least a moderate level of medical decision-making). Take-home point: The physician is ultimately responsible for selecting the CPT and ICD-10 codes. When staff feel the codes are incorrect, they must notify the physician and have a discussion before any change is made. These conversations can be great teaching opportunities.

4. Do participate in payer listservs. Auditors expect your documentation to be in line with the policy that was in place at the time of the patient encounter. The challenge is that each payer frequently updates its policies, and once the policy change has been published the payer has fulfilled its obligation to inform you of the change. To stay current on payers' latest payment policies, participate in their free listservs. As soon as you learn about a policy change, make sure you share it with all who need to know, including physicians, technicians, scribes, billers, and coders. You also should visit aao.org/lcds to review the Medicare Part B local coverage determinations (LCDs) for each Medicare Administrative Contractor (MAC) that you work with.

5. Don't apply one payer's rules or perceived rules to all other payers. Each payer can, and often does, have its own requirements—even among MACs. A commercial payer with several carve-out plans often has rules unique to one of the carve-outs due to negotiations with businesses.

6. Do have a good contact at each payer. Ideally, your relationship with each payer's representative should be such that he or she would want to become your patient and refer family and friends.

* Drs. Howser and Kildare are fictional, but they're not the fictional TV doctors that you're thinking of.

BY **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT.

Further Resources

Demonstrate coding competency. Visit aao.org/ocs to learn about the Ophthalmic Coding Specialist (OCS) and OCS Retina (OCSR) exams.

Be audit ready. Use the free web audit resource at aao.org/practice-management/regulatory/audit-toolkit (free benefit for Academy and AAOE members). And go to aao.org/store for the Audit Survival Toolkit webinar (product #01250098U) and the Coding Audit Success Toolkit (product # 120444V).

MIPS—What's New for 2019, Part 1: Scoring, Bonuses, Penalties, and PI

In November, Centers for Medicare & Medicaid Services (CMS) announced significant changes to the Merit-Based Incentive Payment System (MIPS) for the 2019 performance year. Part 1 of this two-part series reviews general program changes and the restructuring of promoting interoperability (PI), which is the EHR-based performance category. Part 2 looks at the other three performance categories.

Scoring, Penalties, Bonuses

MIPS final score—quality's contribution is down, cost's is up. In 2021, your payments for Medicare Part B services will be adjusted up or down based on your 2019 MIPS final score, which is a composite score that can range from 0 to 100 points and is based on up to 4 performance category scores:

Quality score is weighted at 45% (down from 50% in 2018), meaning it can contribute up to 45 points to your 2019 MIPS final score.

PI score is weighted at 25% (same as 2018).

Improvement activities score is weighted at 15% (same as 2018).

Cost score is weighted at 15% (up from 10% in 2018). CMS states that it expects to continue boosting cost's weight by 5%, and reducing quality's weight by 5%, every year until they are each weighted at 30% of the final score.

Your scores can be reweighted. Like in 2018, the relative weights of these four scores can be adjusted. For example, if you qualify for a PI exception, PI's weight in your 2019 MIPS final score will be reduced to zero, and quality's weight will be increased to 70%.

Final score bonus points—one bonus has been retained, the other moved to quality. As in 2018, a complex patient bonus (0-5 points) can boost your MIPS final score. However, the small practice bonus has been moved from the MIPS final score to the quality performance category score.

Table 1: Bonuses and Penalties

2019 MIPS Final Score	2021 Payment Adjustment
0-7.5 points	-7% penalty
7.51-29.99 points	Less than -7% penalty*
30 points	Neutral (no bonus; no penalty)
30.01-74.99 points	Small bonus*
75-100 points	Small bonus* + exceptional performance bonus*

* This penalty and these two bonuses will be based on linear sliding scales. For each of the bonuses, for example, the higher your 2019 score, the greater the positive adjustment that will be applied to your 2021 payments.

Negative payment adjustments may be higher. As shown in Table 1, if your 2019 MIPS final score is less than 30 points, your payments for Medicare Part B services in 2021 will incur a negative payment adjustment; if you score 7.5 points or less, those payments will be subject to the maximum 2021 penalty of -7%. (By comparison, during the 2018 performance year, scores of less than 15 points will result in a negative payment adjustment in 2020, with scores of 0-3.75 points resulting in the maximum 2020 penalty of -5%.)

How the positive payment adjustments are funded. The performance bonus for clinicians who exceed 30 points is funded by the reduction in payments to those who score less than 30 points. The exceptional performance bonus for scoring at least 75 points is funded by a separate $500 million bonus pool.

No change in performance periods. For 2019, the PI and improvement activities performance categories each require a performance period of at least 90 consecutive days; the performance period for quality and cost is the full calendar year. CMS also plans to maintain the same performance periods in the 2020 performance year.

Avoiding the payment penalty is harder now that you must score at least 30 points. Scoring 100% for

BY **CHRIS MCDONAGH,** SENIOR EDITOR, *EYENET,* AND **JESSICA PETERSON, MD, MPH,** ACADEMY MANAGER OF QUALITY AND HIT POLICY.

improvement activities contributes 15 points to your MIPS final score. For the 2018 performance year, that would have been enough to avoid the 2020 MIPS payment penalty. But if you max out your improvement activities score in 2019, you will still have to score points for quality measures and/or PI measures in order to get the 30 points that are needed to avoid a 2021 penalty.

Special scoring for clinicians who join a practice late in the year. If you join a practice in the last three months of 2019, CMS will assume that you won't have enough measures available to you to participate as an individual in MIPS. What does this mean for your score? If you join a newly formed practice (established after Oct. 1, 2019) or if you join an established practice where the clinicians are reporting as individuals, CMS will award you a MIPS final score of 30 points, which means you would get a neutral payment adjustment in 2021 (no bonus and no penalty). If you join an established practice that is reporting as a group, you would get the practice's group score.

MIPS Eligibility Criteria

More clinicians are eligible to participate. CMS expanded the definition of MIPS eligible clinician to include six additional types of clinician, such as physical therapists and occupational therapists. None of them are likely to be found in an ophthalmology practice.

Low-volume clinicians now have an opt-in option. In 2018, you were excluded from MIPS if you fell below either of two low-volume thresholds. For 2019, CMS added an opt-in option: You can choose to participate in MIPS if you fall below at least one, but not all, of the low-volume thresholds, which now include a third threshold: Providing 200 covered professional services to Medicare Part B patients. At time of press, CMS had not yet set a deadline for opting in. If you do opt in for 2019, you will be subject to a payment adjustment in 2021. And you can't change your mind—the decision is irrevocable until the next performance year.

MIPS Determination Periods

Several determination periods are consolidated into one. Each year, CMS uses Medicare data to make several determinations about your MIPS eligibility and status. Two examples: Do you qualify for a low-volume exclusion? Is your practice considered small or large? For 2019, CMS will make most of these decisions based on data from a two-segment determination period that is aligned with the government's fiscal year:

- Oct. 1, 2017–Sept. 30, 2018 (plus a 30-day claims run out)
- Oct. 1, 2018–Sept. 30, 2019 (no claims run out)

If, for example, you fall below a low-volume threshold in the 2017/2018 time segment, you would qualify for the low-volume exclusion even if you exceed the same threshold in the 2018/2019 time segment.

What has changed? Previously, some of these decisions were based on a Sept. 1–Aug. 31 timeline; they had differences in their claims run-out policies; and the practice-size determination was based solely on historic data.

Check your quarterly snapshots. During the determination period's second time segment (Oct. 1, 2018 –Sept. 30, 2019), CMS hopes to provide you with quarterly snapshots that would show—based on the data available at that point in time—what the agency's provisional status and eligibility determinations would be for you. Although the final determinations won't be made until after Sept. 30, 2019, these snapshots will give you a sense of what those final decisions are likely to be.

Promoting Interoperability

The EHR-based performance category has had a major overhaul. CMS has restructured PI, which now has a new scoring methodology. The agency also has made some changes to the PI measures, with some measures being renamed, modified, and combined.

You may need to upgrade your EHR system. In 2018, you could use an EHR system that was certified as a 2014- or 2015-edition certified EHR technology (CEHRT); in 2019, your EHR must be a 2015-edition CEHRT.

Some PI measures have been removed. CMS eliminated the 2018 PI transition measure set altogether, and it also eliminated four measures from the PI measure set: Patient-Generated Health Data; Patient-Specific Education; Secure Messaging; and View, Download, or Transmit.

PI is now arranged around four objectives: 1) e-Prescribing; 2) Health Information Exchange; 3) Provider to Patient Exchange; and 4) Public Health and Clinical Data Exchange. Each objective has at least one measure associated with it (see Table 2).

Fall short with even just one measure and your PI score will be zero. In order to earn any score for the PI performance category, you must either 1) report a numerator of at least 1 or, if an exclusion is available, 2) claim an exclusion for each of the required measures. If you fail to do that, your PI score will be zero.

Exclusions are available for most of the PI measures. For example, there are two exclusions available for the Support Electronic Referral Loops By Sending Health Information measure. If you qualify for either of those exclusions, the 20 points for that measure would be reallocated to another measure.

Not all PI measures have exclusions. There is no exclusion for the Provide Patients Electronic Access to Their Health Information measure.

The two new opioid-related measures are optional in 2019, and therefore, they don't need an exclusion.

For most PI measures, you will be scored based on your performance rate. You can, for example, score up to 10 points for the e-prescribing mea-

Check Your RA in 2019

If you participated in MIPS in 2017, your 2019 payments for Medicare Part B services could be subject to a payment adjustment, which will be flagged in your remittance advice (RA). To make sure you are paid correctly, you will need to apply an internal charge to offset the adjustment. Learn more at aao.org/medicare/2019-MIPS-payments-understanding-remittance-advice-codes.

Table 2: 2019 Promoting Interoperability (PI) At a Glance

To get a PI score, you must perform all nine of these steps: ❶ have 2015-edition CEHRT; ❷ submit a "Yes" for the Security Risk Analysis attestation; ❸ submit a "Yes" for the Prevention of Information Blocking attestation; ❹ submit a "Yes" for the ONC Direct Review attestation; and satisfy the reporting requirements ❺ through ❾, as shown below. (The minimum performance period for the measures listed below is 90 consecutive days.)

Objective	Reporting Requirements	2019 PI Measure	Equivalent 2018 Measure(s)	Points	
e-Prescribing	❺ Report a numerator of at least 1 or claim an exclusion* for this measure:	e-Prescribing	e-Prescribing	Up to 10	Performance rate–based scoring
	These two opioid-related measures are optional.	Query of Prescription Drug Monitoring Program (PDMP)		Up to 5	
		Verify Opioid Treatment Agreement		Up to 5	
Health Information Exchange	❻ Report a numerator of at least 1 or claim an exclusion* for this measure:	Support Electronic Referral Loops by Sending Health Information	Send a Summary of Care	Up to 20	
	❼ Report a numerator of at least 1 or claim an exclusion* for this measure:	Support Electronic Referral Loops by Receiving and Incorporating Health Information	Request/Accept Summary of Care	Up to 20	
			Clinical Information Reconciliation		
Provider to Patient Exchange	❽ Report a numerator of at least 1 for this measure:	Provide Patients Electronic Access to Their Health Information	Provide Patient Access	Up to 40	
Public Health and Clinical Data Exchange	❾ (a) Report two measures, or (b) report one measure for two clinical data registries or public health agencies, or (c) report one measure and claim one exclusion, or (d) claim two exclusions.*	Immunization Registry Reporting	Immunization Registry Reporting	0 or 10	"Yes" or "no" attestation
		Electronic Case Reporting	Electronic Case Reporting		
		Public Health Registry Reporting	Public Health Registry Reporting		
		Clinical Data Registry Reporting	Clinical Data Registry Reporting		
		Syndromic Surveillance Reporting	Syndromic Surveillance Reporting		
2019 PI score is sum of your measure scores (capped at 100 points, and reported as a percentage)				0-100	

* Note: If you claim exclusions, points may be reallocated. For example, if you claim *two* exclusions for the Public Health and Clinical Data Exchange objective, its 10 points would be reallocated to the Provider to Patient Exchange objective.

sure; if your performance rate is 80%, you would score eight points. However, the scoring is not performance rate–based for the five measures in the Public Health and Clinical Data Exchange objective (see Table 2).

The Security Risk Analysis measure. In 2019, as in 2018, this measure is mandatory—but you no longer earn points for it. The analysis must be done at some point during 2019, but it doesn't have to take place during your 90-day PI performance period.

Who has to participate in PI? As in 2018, some clinicians may be excused from PI. The six new types of MIPS eligible clinicians are automatically excluded from PI.

Hardship exceptions. CMS is continuing its significant hardship policy for PI. For example, if you are in a small practice, you may be excused from PI if you successfully apply for a significant hardship exception.

Keys to MIPS Success

Use the IRIS Registry (aao.org/iris-registry). This free member benefit is eye care's tool of choice for MIPS.

Stay tuned. This article reflects the Academy's knowledge of the 2019 regulations at time of press, but CMS payment policies can change. For MIPS updates, visit aao.org/medicare *and* check your email each week for Washington Report Express and, if you are in AAOE, Practice Management Express.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

AAO 2019

Submit an Abstract

Instruction Courses and New Skills Labs
December 13, 2018 – January 8, 2019

Papers/Posters and Videos
March 7, 2019 – April 9, 2019

Join Us in San Francisco

AAO 2019 October 12 – 15

Subspecialty Day October 11 – 12

AAOE Program October 11 – 15

Blaze the trail to a future built on technology and innovation – or master the teachings from ophthalmic visionaries.

Watch this short video at **aao.org/2018** to celebrate AAO 2018.

Where All of Ophthalmology Meets®

aao.org/2019

Inspire!

Protecting Sight. Empowering Lives.®

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Academy Makes Great Strides Toward Museum's New Home

During AAO 2018, the 15th annual Orbital Gala was held at the Chicago Cultural Center under the famous Tiffany Dome. More than 350 guests attended the '60s-themed party and auction. All proceeds benefited the Foundation's newest fundraising project: building a permanent home for the Museum of Vision at the Academy headquarters, located in the heart of the tourist-rich San Francisco Fisherman's Wharf. For over 30 years, the Museum of Vision committee has dreamed of permanently and publicly displaying the Museum's artifacts.

David W. Parke II, MD, Academy CEO, introduced the Museum of Vision project by honoring recent Museum donors **Stanley M. Truhlsen, MD,** and **Michael F. Marmor, MD,** as well as Museum Director **Jenny Benjamin** and Museum Committee members **Norman B. Medow, MD, FACS, Jay M. Galst, MD, Andrzej Grzybowski, MD, Jacqueline A. Leavitt, MD, James G. Ravin, MD,** and **Richard B. Rosen, MD.** All received a standing ovation.

Museum donors. Dr. Parke said, "Most people don't know what ophthalmology is or how ophthalmologists protect sight. Thanks in large part to generous donations from Dr. Truhlsen and Dr. Marmor, the new Museum of Vision will be the first of its kind where the public can go to learn about sight, to see it, to touch it."

Dr. Truhlsen, an Academy Past President, kicked off major donations to the Museum in early 2018 and began to pave the way for this project's realization. Later in the year, Dr. Marmor, professor of ophthalmology at Byers Eye Institute at Stanford, made an additional sizeable contribution, pushing fundraising efforts toward their $12 million goal. To show appreciation for the generosity and dedication of Drs. Truhlsen and Marmor, the Museum will be named in their honor.

MUSEUM VISIONARIES. *Dr. Parke (center) recognized Museum donors Dr. Truhlsen (left) and Dr. Marmor (right) at the Orbital Gala, which took place in the Chicago Cultural Center during AAO 2018.*

Stressing the importance of a Museum, Dr. Truhlsen said, "For thousands of years, ophthalmology has pushed the envelope, discovering breakthrough innovations to protect sight. The Museum is the vehicle by which our heritage remains both relevant and inspiring, promoting continued discovery and advancement."

Dr. Marmor added, "By making the eye fascinating and our management of disease accessible, people will indeed understand our profession better—and by bringing our history into view, the evolution of knowledge and technology that makes modern ophthalmology so powerful will become evident."

Gala donations. Gala attendees also donated to the Museum in two ways. First, attendees participated in a silent auction. Second, **Christie L. Morse, MD,** the Foundation Advisory Board Chair, took the stage and provided step-by-step instructions for using the Donate Now button accessible through attendees' smartphones. Overall, proceeds from the gala brought in $130,000 in net revenue to benefit the museum. The Museum is expected to open during AAO 2019.

AMERICAN ACADEMY OF OPHTHALMOLOGY®

TAKE NOTICE

Don't Miss the Jan. 15 Deadline for MIPS

If you are using the IRIS Registry (Intelligent Research in Sight) to report the Merit-Based Incentive Payment System (MIPS), Jan. 15 is a key date on two counts.

1. Finish manually entering your MIPS information. This deadline applies if you are using the IRIS Registry web portal to manually report quality measures, promoting interoperability (PI) measures, or improvement activities. If you successfully integrated your electronic health record (EHR) system with the IRIS Registry, your MIPS quality data are automatically extracted from your EHRs, but you must report PI measures and improvement activities manually.

2. Submit a signed data-release consent form. The IRIS Registry won't submit your MIPS data to Centers for Medicare & Medicaid Services unless it has received the signed consent form. If you are reporting as an individual, you should sign your own consent form; if you are reporting as part of a group, you can submit a single consent form, which can be signed by the administrator. You must submit a new consent form each year, and you can do so via the IRIS Registry dashboard. For instructions, see aao.org/consent-form.

New for 2018. If you are manually reporting patients for a quality measure, you must submit to the IRIS Registry the total number of patients eligible, excluded, and excepted from that measure.

To learn more about the IRIS Registry and MIPS, see aao.org/iris-registry and aao.org/medicare.

Honor Your Colleagues

To recognize the achievements of ophthalmologists who have made incredible contributions to ophthalmology, the Academy would like your help in nominating recipients for the following awards.

Laureate Recognition Award. This award honors an outstanding ophthalmologist whose significant scientific contribution to the field has shaped modern ophthalmology. The Academy is accepting nominations through Jan. 31, 2019, for the 2019 award, with nomination forms available at aao.org/about/awards/laureate#nominations.

2020 International Blindness Prevention Award. Established in 1992, this award is presented at the Academy's annual meeting to honor an individual who has made significant contributions to the prevention of blindness or restoration of sight. Nominate a colleague for the 2020 award by Jan. 30, 2019, by visiting aao.org/about/awards/blindness-prevention.

Outstanding Humanitarian Service Award. This award recognizes Academy fellows and members for outstanding contributions to humanitarian efforts, such as participation in charitable activities, care for the indigent, and community service. It acknowledges those who have performed above and beyond the normal duties of an ophthalmologist. All nominations for the 2019 award must be received by March 8, 2019. To submit a nomination, visit aao.org/about/awards/humanitarian.

Follow @AAOjournal for the Latest Articles

Stay up-to-date on research from *Ophthalmology, Ophthalmology Retina,* and *Ophthalmology Glaucoma* via the @AAOjournal Twitter handle. New content is posted every day, including articles in press, fascinating "Pictures and Perspectives," thought-provoking editorials, and new issue alerts.

LDP CLASS XX. *The Academy's 20th class of the Leadership Development Program (LDP) graduated in October 2018 during the annual meeting.*

MEMBERS AT LARGE

Leadership Development Program Welcomes Its 21st Class

The Academy's Leadership Development Program (LDP) XX held its graduation session during AAO 2018 in Chicago. Concurrently, the Academy's 21st LDP (LDP XXI) class met in an orientation session along with participants in the complementary Curso de Liderazgo class of the Pan-American Association of Ophthalmology. The joint session was led by LDP Director **Linda M. Tsai, MD,** and Curso Director **Zélia M. Corrêa, MD, PhD.**

The Academy's 21st LDP class includes its first participant from Africa, **Feyi Grace Adepoju, MD.** Dr. Adepoju is from Nigeria and was nominated by the African Ophthalmology Council. She joins 18 other ophthalmologists nominated by state, subspecialty, and specialized interest societies and chosen in a competitive selection process for the yearlong program.

To learn more, visit aao.org/about/leadership-development.

Academy Hall of Fame Award Recipient Announced

Basil S. Morgan, MD

During the Oct. 28 Fall Council meeting in Chicago, **Basil S. Morgan, MD,** of Maryland was recognized by the Academy's Secretariat for State Affairs as the 2018 Hall

of Fame Award recipient. The Hall of Fame Award annually recognizes an ophthalmologist for a long-term commitment to state advocacy efforts.

Heed-Gutman Award

Carol L. Shields, MD, received the 2018 Heed-Gutman Award during the Society of Heed Fellows Luncheon in Chicago during AAO 2018. Dr. Shields is currently director of the Oncology Service at Wills Eye Hospital and professor of ophthalmology at Thomas Jefferson University in Philadelphia. Dr. Shields was a Heed Fellow from 1987-1988.

ACADEMY RESOURCES

New Research to Benefit Your Patients

Focal Points curates the most crucial advances so you can focus on findings that make a significant difference for your patients. Each issue of *Focal Points* features quick tips to help you apply new research. In addition to reading on paper or digitally, you can download the new monthly audio version.

Subscribe to *Focal Points Digital* to get a new issue every month, plus access to the digital archive. Print subscribers get 12 print issues, plus all the benefits of *Focal Points Digital.*

Subscribe at aao.org/focalpoints.

Code Confidently With 2019 Coding Tools

Sharpen your coding skills with the Academy and AAOE's new comprehensive coding tools:

- Coding Audit Success Toolkit
- 2019 Ophthalmology Updates Webinar
- Coding for Anterior Segment Surgical Complications recorded webinar.

Also, check out the newly updated suite of 2019 coding reference and training books for comprehensive and subspecialty practices.

For more information, visit aao.org/codingtools.

Ophthalmology Business Summit

Creating value for your practice while effectively serving patients is more challenging than ever. Join the Academy's business-focused "boot camp" and uncover actionable strategies that can immediately impact your practice's revenue and growth. Physician leaders and senior administrators can attend the Ophthalmology Business Summit individually or as a team to benefit from an intensive two-track program developed by notable business experts and Academy leaders. Attend March 23-24, 2019, in Chicago and position your practice for success.

Find the complete curriculum at aao.org/business-summit.

D.C. REPORT

CMS Changes for 2019

On Nov. 1, 2018, the Centers for Medicare & Medicaid Services (CMS) finalized several important Medicare policies affecting physicians. The agency issued a combined final rule that includes the 2019 Medicare physician fee schedule, along with changes to the Quality Payment Program. This includes changes to the Merit-Based Incentive Payment System (MIPS).

Here are the key changes that are most likely to impact your practice:

Evaluation and Management (E&M) services. CMS will change how E&M is reimbursed, collapsing the payment levels from five to three. The changes won't take place until 2021. This delay is a major Academy win, as are the significant improvements over the earlier proposals. These improvements resulted from a major Academy campaign to educate the Trump administration and key members of Congress about the impact the earlier proposal would have had on patient care. By delaying the policy until 2021, CMS is acknowledging that significant transition time is needed.

The E&M change also rejected the proposed multiple procedure payment reduction that drew Academy objections because it would have resulted in a significant payment cut to our profession's subspecialists, especially those who bill intravitreal injections with the —25 modifier.

One significant E&M change is effective as of Jan. 1, 2019: documentation reductions. CMS will only require patient-history documentation to be focused on the interval history since the previous visit. The agency also eliminated the requirement that physicians redocument information that has already been entered into the record by practice staff or that has been entered into a form by the patient.

Valuation of CPT codes. In the initial proposed rule, CMS had valued eight ophthalmic codes at less than the level recommended by the RVS Update Committee (RUC). The Academy presented CMS with compelling evidence in support of the RUC's valuations, and CMS did adopt the RUC's valuation for one code—67505 *Retrobulbar injection; alcohol*—but not for the other seven codes, which cover foreign body removal, anterior segment or subconjunctival injections, pachymetry, and electroretinography.

CMS had initiated an ongoing, targeted survey of global surgical payments. It won't be making any payment adjustments based on that survey for 2019, but it is continuing to evaluate the data that are being collected.

For changes to the Merit-Based Incentive Payment System (MIPS), see page 49.

MEETING MATTERS

AAO 2019 in San Francisco

Attend AAO 2019, Oct. 12-15, preceded by Subspecialty Day, Oct. 11-12, at Moscone Center in San Francisco. Be inspired in the City by the Bay as you experience the world's most comprehensive ophthalmic meeting. AAO 2019 will feature hundreds of courses and sessions on topics ranging from cataract complications to ophthalmic applications of artificial intelligence.

For more information, visit aao.org/2019.

Be Part of AAO 2019

The AAO 2019 online abstract submitter for instruction courses or new Skills Transfer labs is closed as of Tuesday, Jan. 8. However, there is still time to prepare your paper, poster, or video abstract for AAO 2019. The online abstract submitter opens March 7 and closes April 9, 2019.

For more information, visit aao.org/presentercentral.

AAO 2018 Meeting Archives

Missing a handout from AAO 2018? Want to view scientific posters or a video? Go to Meeting Archives to find these resources and more, including Subspecialty Day syllabi, the *Meeting Program,* and exhibition information.

Visit the Meeting Archives at aao.org/aao-archives.

FOR THE RECORD

Election Results

On Oct. 29, 2018, voting opened for three positions on the 2019 Board of Trustees.

The results are as follows:

- President-Elect: **Anne L. Coleman, MD, PhD**
- Senior Secretary for Clinical Education: **Christopher J. Rapuano, MD**
- Trustee-at-Large: **Judy E. Kim, MD**

For more information about the elections, visit aao.org/about/governance/elections.

Nominations for the Academy Board

By Keith D. Carter, MD

As Past President of the Academy, it is my privilege to serve as Chairman of the Academy's Nominating Committee in 2019. This committee represents a variety of interests within the Academy and is charged with identifying appropriate candidates for the open positions on the 2020 Board of Trustees.

The committee is interested in identifying leaders in our profession with experience in confronting the critical issues facing organized medicine and who reflect the strength and diversity of our members. The Academy's leaders should be knowledgeable, experienced, and prepared to devote the time and energy required by a large organization in these challenging times. This work is both demanding and rewarding for those interested in helping to assure the Academy's success and responsiveness to members. With these characteristics in mind, I ask you to assist the committee by suggesting appropriate candidates for the following positions in 2020:

President-Elect (to serve as President in 2021). Nominees should have leadership experience within the Academy as well as demonstrated leadership qualities in clinical practice, in their own ophthalmic communities, and in other medical or ophthalmological organizations.

Senior Secretary for Ophthalmic Practice (three-year term). This senior secretary coordinates the programs and activities relating to the management and practice of ophthalmology.

Secretary for Annual Meeting (three-year term). This secretary is responsible for all Academy programs at the annual meeting and Subspecialty Day. **Maria Aaron, MD,** is currently serving the third year of her term and is eligible for a second term.

Two Trustees-at-Large (four-year term). These individuals should be Academy Fellows who demonstrate strong leadership potential and would be able to represent and articulate the needs and concerns of the membership to the Academy board.

Public Trustee (a renewable three-year appointment). The Bylaws allow the board to appoint up to three public trustees. A public trustee is an advisor to and member of the Board of Trustees. Public trustees provide insight on how ophthalmology can better work with the rest of medicine, the public, government, and industry. The nominating committee will be pleased to receive suggestions for individuals who may be physicians from other medical specialties or leaders in industry, government, public policy, or advocacy. Currently **Paul B. Ginsburg, PhD,** is completing his fifth term in 2019 and is eligible for a sixth term.

Thank you for your interest and participation in this process. Membership participation is vital, not only for the Academy, but also for our collective goals of being able to provide appropriate, accessible, and affordable eye care to the public. On behalf of the Nominating Committee, I look forward to receiving your suggestions as we seek to identify our profession's future leaders.

Send your confidential suggestions by Jan. 31, 2019, to Keith D. Carter, MD; Nominating Committee Chair, American Academy of Ophthalmology, P.O. Box 7424, San Francisco, CA 94120-7424. Suggestions can also be emailed to nominate@aao.org or faxed to 415-561-8526.

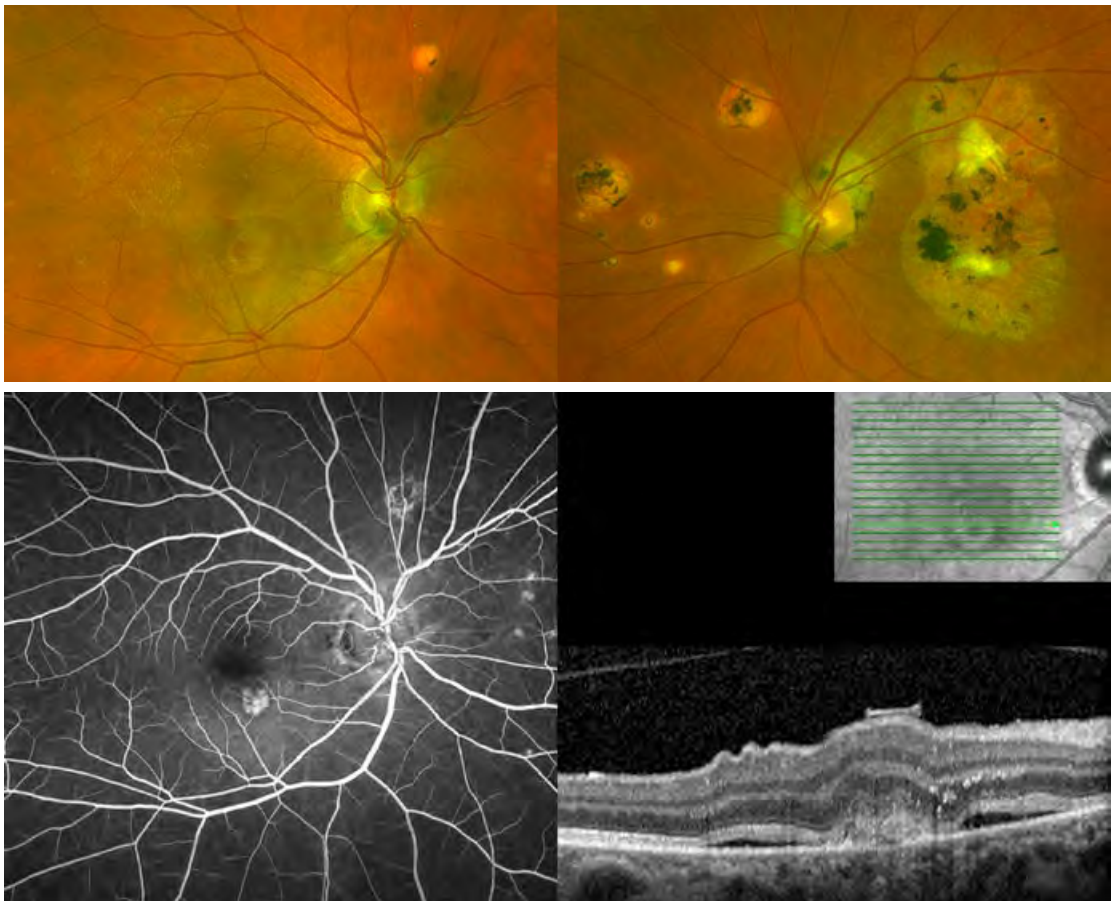
For more information, visit aao.org/about/governance/board-nominations.

ABOUT THE NOMINATING COMMITTEE

The Academy nominating process has been carefully crafted to be inclusive, fair, and efficient. This process encourages a broad base of nominations from the entire Academy membership. The Nominating Committee composition is delineated by the Bylaws, and it considers a number of factors when screening potential candidates. These include integrity, ophthalmology leadership ability, special expertise, past committee and leadership experience and performance, and knowledge and interest in the multitude of issues currently facing ophthalmology. In addition to considering nominations from the current year, the committee reviews prior-year nominations to ensure a wide range of potential candidates for each position. Following months of confidential deliberations, the committee presents final recommendations to the Board of Trustees for approval. This single-candidate method avoids the loss of valuable future leaders, as there are no public "losers" in the election. Often, those considered but not selected for an open position one year become the nominees of choice in a future year.

MYSTERY IMAGE

BLINK

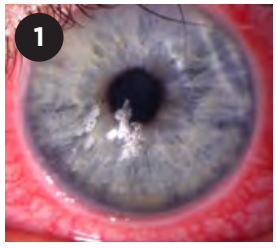


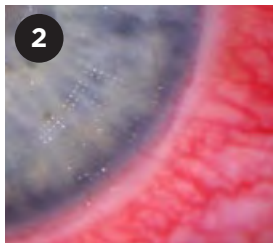
Siva S. Radhakrishnan Iyer, MD

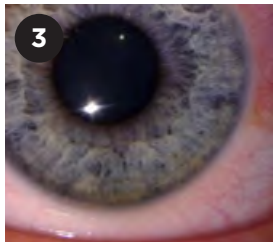
WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments and get the answer to last month's mystery.*

LAST MONTH'S BLINK

Contact Lens Overwear







A 31-year-old man was referred for "epithelial edema" and linear crystal-like deposits that could not be debrided in the left cornea (Fig. 1). The patient admitted to wearing contacts for 60 consecutive days without removal and reported possible corneal abrasion of the left eye two weeks earlier when he unsuccessfully attempted to replace his monthly disposable soft lenses. At presentation, visual acuity (VA) was 20/50 in the right eye with his contact lens and 20/400 with his contact lens in the left eye, which additionally had 4+ diffuse conjunctival injection with 360 degrees of limbal blanching.

High-magnification inspection revealed a numerical dot-matrix pattern in the far inferior-temporal periphery (Fig. 2) of his left cornea consistent with a retained soft contact lens. Remarkably, the conjunctiva had grown over the top of the lens (seen as the area of limbal blanching). After blunt dissection with a Weck-Cel sponge, the edge of the lens was freed and then removed. He was started on preservative-free artificial tears and prophylactic antibiotic drops and instructed to discontinue contact lens wear. At his one-week follow-up visit, his best-corrected VA was 20/25 with no further pain, a completely clear cornea, and markedly improved conjunctival injection and chemosis of the left eye (Fig. 3).

WRITTEN AND PHOTOGRAPHED BY **RUBEN KURUVILLA, MD,** LASER EYE SURGERY OF ERIE, ERIE, PA.

DEXYCU (dexamethasone intraocular suspension) 9%, for intraocular administration
Initial U.S. Approval: 1958

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

Prolonged use of corticosteroids including DEXYCU may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

5.2 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids.

5.3 Exacerbation of Infection

The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection.

5.4 Cataract Progression

The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Increase in Intraocular Pressure *[see Warning and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Infection Exacerbation *[see Warnings and Precautions (5.3)]*
- Cataract Progression *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively *[see Data in the full prescribing information]*.

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use

Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between older and younger patients.

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

NEW The first and only FDA-approved, single-dose, sustained-release, intracameral steroid for the treatment of postoperative inflammation[1-3]

With a single injection at the end of cataract surgery, anti-inflammatory efficacy begins as early as day 1 and continues through day 30[1*]

- The percentage of patients who received DEXYCU (517 mcg) who had anterior chamber cell clearing on day 8 was 60% (N=94/156) vs 20% (N=16/80) in the placebo group[1]
- The cumulative percentage of subjects receiving rescue medication of ocular steroid or nonsteroidal anti-inflammatory drug (NSAID) at day 30 was significantly lower in the DEXYCU 517 mcg treatment group (20%; N=31/156) compared to placebo (54%; N=43/80)[1]

Approved & Available Soon

DEXYCU™
(dexamethasone intraocular suspension) 9%

Visit DEXYCU.com for more details.

*DEXYCU was studied in a randomized, double-masked, placebo-controlled trial. Patients received either DEXYCU or a vehicle administered by a physician at the end of the surgical procedure. The primary endpoint was the proportion of patients with anterior chamber cell clearing (cell score = 0) on postoperative day 8.

INDICATION AND USAGE

DEXYCU™ (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

- Prolonged use of corticosteroids, including DEXYCU, may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision
- Steroids should be used with caution in the presence of glaucoma

Delayed Healing

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids

Exacerbation of Infection

- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures
- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection

Cataract Progression

- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

ADVERSE REACTIONS

- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. DEXYCU™ (dexamethasone intraocular suspension) 9% full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. July 2018. **2.** Donnenfeld E, Holland E. Dexamethasone intracameral drug-delivery suspension for inflammation associated with cataract surgery: a randomized, placebo-controlled, phase III trial. *Ophthalmology*. 2018;125(6):799-806. **3.** Data on file. EyePoint Pharmaceuticals, Inc.

EyePoint™ PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472

10/2018
DEX0031