

# Medscape<sup>®</sup>

BUSINESS OF MEDICINE

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Physicians

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## NEW ETHICAL CHALLENGES AND HOW TO COPE

P. 9

OFFICE BOTTLENECKS? HERE ARE SOLUTIONS P. 13

AVOID MEDICAL BOARD DANGERS P. 20 • HOW PERVERSIVE IS SEXUAL HARASSMENT OF PHYSICIANS? P. 6



# HELP SHATTER **HCV** BY **LINKING** YOUR PATIENTS TO **CURE**



**A PROMPT, QUALITY REFERRAL IS VITAL TO GIVE  
YOUR PATIENTS THE BEST CHANCE OF BEING CURED.<sup>1</sup>**

Your role in HCV makes an impact on patients' lives.

HCV = hepatitis C virus

Cure, or sustained virologic response (SVR12), is defined as undetectable levels of HCV in the blood at 12 weeks after completion of therapy.<sup>1,2</sup>

**References:** 1. AASLD, IDSA, IAS-USA. <http://www.hcvguidelines.org>. Accessed September 21, 2017. 2. HHS/FDA/CDER. Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. November 2017. 3. Holmberg SD et al. *N Engl J Med*. 2013;368(20):1859-1861. 4. McGowan CE et al. *Liver Int*. 2012;32(suppl 1):151-156.



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AS MANY AS **1/3** OF  
**THOSE WHO TESTED HCV  
POSITIVE** DID NOT RECEIVE  
FOLLOW-UP CARE<sup>3</sup>

**TREATMENT DELAYS CAN  
INCREASE THE MORBIDITY  
AND MORTALITY RISKS  
OF HCV<sup>1</sup>**



**TAKE ACTION:  
LINK ALL OF YOUR DIAGNOSED  
HEPATITIS C PATIENTS TO CARE**

**Inform and educate** your patients that HCV often can progress without symptoms and that the earlier treatment is initiated, the more likely they can achieve cure<sup>1</sup>

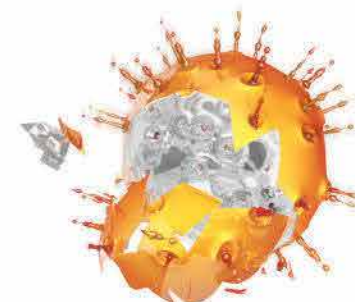


**Find and schedule the appointment** with a provider who treats HCV and is conveniently located for your patients



**Follow up** to ensure the patient saw a treatment provider because **25% to 50%** of HCV patients miss their first appointment<sup>4</sup>

**Consider treating HCV** in your practice to help mitigate drop-off in follow-up care



Find information, tools, and educational resources on screening, diagnosing, and referral at **HCVcanbecured.com/J13** or download the **RETHINK HCV app** from the App Store or Google Play.



# ETHICAL DECISIONS GET HARDER FOR DOCTORS



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## SOME MEDICAL/ETHICAL DECISIONS CAN AFFECT PEOPLE'S LIVES FOREVER.

Others, while not life-and-death, have a huge impact on patient well-being as well as on doctors' careers and their own sense of integrity.

While the ethical dilemmas that physicians face change over time, there's one that keeps gaining momentum: the conundrum of cost versus care.

Many physicians are being "encouraged"—often through carrot-and-stick tactics—to perform fewer services, cut down on tests, and keep productivity up by holding shorter patient visits.

But many doctors bristle, feeling that certain screening tests could be helpful—and that listening to and taking more time with a patient can uncover important information and strengthen the

physician-patient bond, which can be therapeutic in itself. Doctors are getting pressure from both sides—patients and groups/hospitals—and it's interfering with their sense of right and desire to do the best job they can.

And that's just one of the ethical issues confronting physicians today. Our article "5 New Ethical Dilemmas" describes current issues weighing on the minds of physicians like you, including ones related to new technology. Read the article and let us know whether you can relate.

In the words of Mark Twain: "Always do what is right. It will gratify half of mankind and astound the other." Easy to say, often impractical to do. But it's comforting to at least consider the possibilities.

— *Leslie Kane*

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# SEXUAL HARASSMENT IN THE MEDICAL WORKPLACE

Medscape's Sexual Harassment of Physicians Report 2018 surveyed more than 6,200 physicians and other clinicians to find out whether they had been sexually harassed in the workplace within the past three years. Some key findings:

## > WHO IS BEING HARASSED?

Personally experienced sexual abuse, harassment, or misconduct:

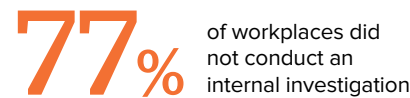


## > WHO WAS THE PERPETRATOR?

1. Physician (47%)
2. Nurse (16%)
3. Medical resident or fellow (4%)
4. Medical student (1%)
5. Nurse practitioner (1%)
6. Other (29%)

## PATIENTS' SEXUAL BEHAVIOR TOWARD PHYSICIANS

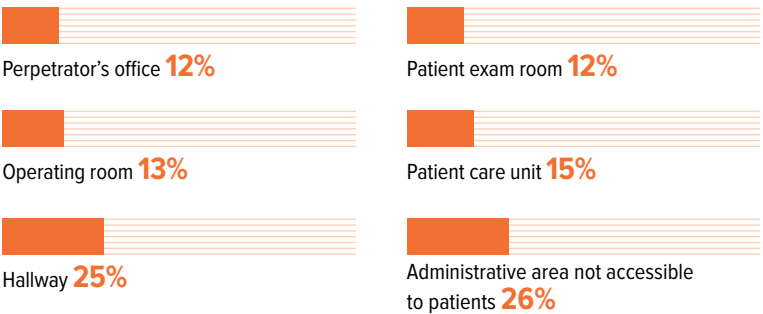
- > Acted in an overtly sexual manner toward you (17%)
- > Asked you out on a date (9%)
- > Tried to touch, grope, or rub against you (7%)
- > Asked you for a sexual encounter (2%)
- > Sent you sexual emails or letters, or gave you provocative photos of themselves (2%)
- > Accused you of making a pass at them or asking for sexual activity (1%)
- > Other (3%)



## HOW WIDESPREAD IS THE HARASSMENT OF PHYSICIANS?

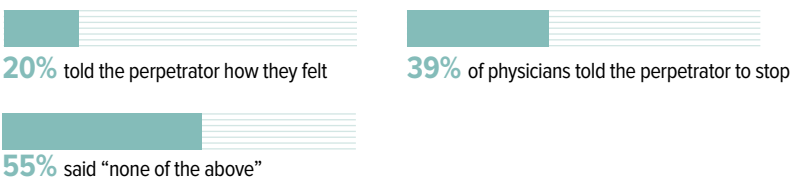


## PHYSICIANS: WHERE DID THE INCIDENT TAKE PLACE?

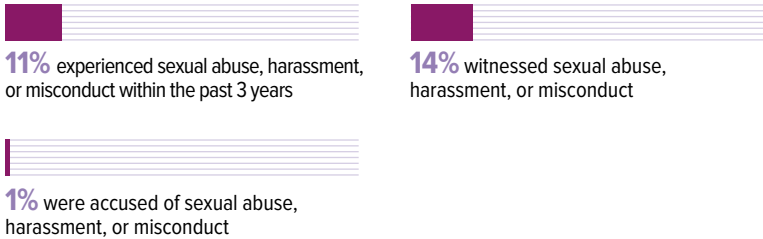


## HOW DID PHYSICIANS RESPOND TO THE PERPETRATOR?

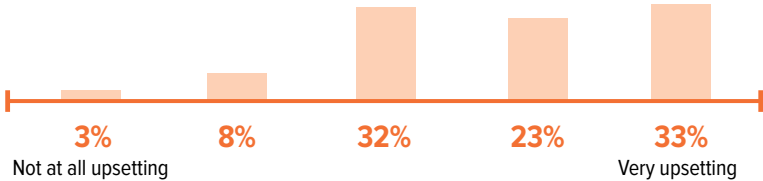
(respondents chose more than one answer)



## HARASSMENT AGAINST NURSES, NPs, AND PAs

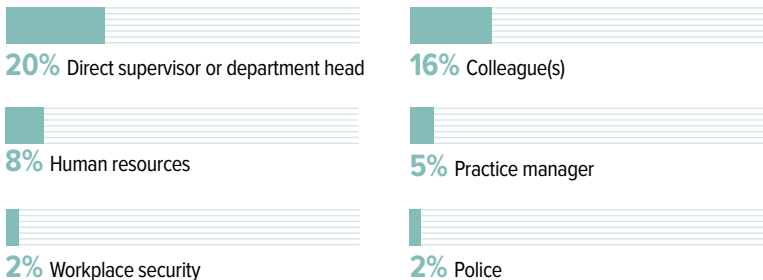


## NURSES, NPs, AND PAs: HOW UPSETTING WAS THE HARASSMENT?



## TO WHOM DID NURSES AND PAs REPORT THE PERPETRATOR?

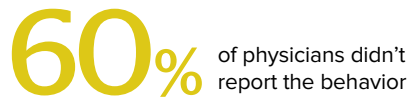
(respondents chose more than one answer)



## WHY DID PHYSICIANS NOT REPORT THE INCIDENT?

(respondents chose more than one answer)

- > Fear of being accused of overreacting (49%)
- > Belief that no action would be taken (45%)
- > Fear of retaliation from the perpetrator (36%)
- > Fear of not being believed (18%)



## > MOST FREQUENT HARASSING BEHAVIORS

1. Deliberately infringing on body space; standing too close (55%)
2. Sexual comments about anatomy or body parts; leering or sexually looking at body parts (52%)
3. Unwanted groping, hugging, patting, or other physical contact (46%)
4. Being asked repeatedly for a date or given continual unwanted romantic attention (26%)
5. Explicit or implicit propositions to engage in sexual activity (21%)
6. Unwanted sexual text messages or emails from someone at work (16%)
7. Grabbing body parts, forcing self physically (short of rape) (8%)
8. Deliberately fondling himself/herself in my view, flashing, mooning (5%)



## YES OR NO TO REQUESTS FROM FRIENDS AND FAMILY FOR MEDICAL ADVICE?

**Asking for free medical advice seems to be a standard event.** A recent Medscape poll surveyed whether nonpatients asked physicians for medical advice. Forty percent of physician respondents said, “yes, often”; 52% said, “sometimes”; and 8% said, “rarely.”

Professional guidelines discourage doctors from giving medical advice or treatment to family members and nonpatients, but a study published in the *Annals of Family Medicine* suggests that it’s hard to stick to those rules.

Instead, physicians should learn to handle those requests in a safe manner.

Investigators from the Care and Public Health Research Institute at Maastricht University in the Netherlands ran five focus groups of physicians and

asked about their experiences with ad hoc medical requests. “Some settings were considered more practical and confidential for diagnostic purposes than others,” the investigators wrote. For example, “If it’s at a party, then the answer is ‘no,’” one participant noted—in that situation, he or she is not a physician but simply another guest. A party or a family gathering is also not considered private enough to give any medical advice.

“The nature of the request itself seemed to be the most important question for physicians, because it determined the urgency of the situation,” the authors state. Emergency situations overshadowed all other factors because physicians felt it was their duty to respond to the request immediately.



## ➤ SHOULD PHYSICIANS TELL EACH OTHER HOW MUCH THEY EARN?

**Pay transparency—openness about what each person is earning—is getting a lot of attention these days as a way to identify and address pay inequities, particularly those that might stem from bias against women, minorities, or other groups.**

Many people of all professions are averse to discussing their salaries. Some say it’s no one’s business. Others, who may be high earners, don’t want resentment from co-workers or to be accused of favoritism—even if the pay is completely based on performance. And some managers or supervisors say that people whose salary is lower on the basis of their performance simply don’t believe that their performance is not as strong as someone else’s.

In a Medscape poll that asked, “Have you ever revealed your salary to another physician?” **31% said, “Yes, to a physician at my workplace”**; 26% said, “Yes, to a physician outside my workplace”; and 43% said, “No, I’ve never revealed my salary to another physician.”

Salary figures taken out of context can be misleading. Compensation calculations

can be ridiculously complex, says Nick Fabrizio, PhD, Medical Group Management Association principal consultant. **The vast majority of hospitals and practices use formulas that factor in customer satisfaction, citizenship, call schedules, productivity, quality, administrative stipends, and other metrics.** “You may have six or seven different components that make up your compensation, and only one part of it is base salary,” he says.

“People will talk with a friend and say, ‘I’m getting \$50 for a relative value unit [RVU].’ If you’re getting \$40 for an RVU, you feel underpaid,” Fabrizio says. But the doctor earning the \$50 rate may have a chintzy benefits package, whereas the one earning the lower rate may have a fully loaded package that includes a 401(k) match, a week off for continuing medical education, and other perks.

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## THE 7 SERVICES PCPs FORGET TO BILL FOR

**There are times when medical practices perform a service, the physician documents the service, and the service is readily reimbursable, but the practice fails to bill for it.**

Why? There are many reasons: Perhaps the practice doesn’t realize they can get reimbursed; their workflow fails to provide for capturing the service into the electronic health record; or the service is lumped in with another service rather than billed separately, which would provide more reimbursement. Collecting revenue for medical practice services is hard work. Don’t compound the problem by not billing for services performed and documented in the office.

### The most overlooked billing codes:

1. Transitional care management: **CPT codes 99495 and 99496**
2. Certification for home health services: **HCPCS codes G0179 and G0180**
3. Smoking-cessation counseling: **CPT codes 99406 and 99407**
4. Administration of vaccine or other injections: **CPT codes 96372, 90471, 90472, 95115, and 95117**
5. Pulmonary services: **CPT codes 94640 and 94664** (use the appropriate medication and education codes)
6. Fracture care codes: **(many potential CPT codes)**
7. Consults: **(several types of appropriate CPT codes)**



# 5 NEW ETHICAL DILEMMAS

HOW TO DEAL WITH TOUGH CHALLENGES

BY LEIGH PAGE

**ETHICAL DILEMMAS IN MEDICINE GO BACK TO THE ANCIENT GREEKS, BUT NEW ONES ARE ARISING ALL THE TIME.** These new

challenges are spawned by trends, such as the need for doctors to see as many patients as possible, the growth of physician employment, and our growing use of smartphones and other forms of telecommunications.

Here are five new ethical dilemmas that doctors now face—along with suggestions on how to deal with them.

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### 1. LESS TIME WITH PATIENTS MIGHT LEAD TO POORER CARE

**THE DILEMMA:** Physicians are facing growing pressures to keep their visits brief, making it harder in some cases to provide the correct diagnosis and ensure an excellent outcome.

Physicians are under enormous pressure to see as many patients as possible, says Clarence H. Braddock III, MD, vice-dean for education at the David Geffen School of Medicine at the University of California, Los Angeles. “In a high-volume primary care practice, the standard amount of time allotted for each patient is 10 to 12 minutes,” says Braddock, lead author of a 2005 paper, “The Doctor Will See You Shortly: The Ethical Significance of Time for the Patient-Physician Relationship.”

Braddock says that short visits force many doctors to concentrate on immediate biomedical issues, such as dealing with a high blood-pressure reading, rather than exploring psychosocial aspects of the patient’s life.

Time management may not be the answer. Doctors who complain about too little time with patients are often urged to improve their time management skills, but this option is limited if the problem is not having enough time in the first place, Braddock says.

**HOW TO DEAL WITH IT: Listen to all of the patient’s complaints.** Physicians sometimes manage the appointment time by limiting the patient to one or two complaints per visit. Indeed, one doctor went so far as to post a sign saying patients were limited to just one complaint per visit.

Not letting patients bring up all their complaints may mean that you miss the most important one, Braddock says. A better way to deal with patients’ lists of complaints, he says, is to let them run through all of them, then prioritize what needs to be dealt with in the current visit.

### 2. PRESSURE TO REFER IN-HOUSE COULD DENY PATIENTS BETTER CARE

**THE DILEMMA:** Employed physicians may have to balance mandates to keep referrals within the organization with the need to provide patients with high-quality care that is not overly expensive.

One key reason hospitals buy up practices is so more patients will use hospital services. Initially, many hospitals were reluctant to press this expectation with newly acquired practices, but that is changing, according to Theresa Hush, CEO of Roji Health Intelligence, a performance consultant for physician groups, many of which are owned by hospitals.

“We’re seeing more restrictions on doctors to refer within the organization,” she says. “Organizations are tracking referrals and sharing the information with their doctors. Doctors might get reports about referrals that make them look negative—a kind of peer pressure. Getting the physicians to look at their data is one of the important changes.”

**HOW TO DEAL WITH IT: Try to remove the obligation from your contract.** Employers hold more sway over employed physicians’ referrals when they actually have a clause in the employment contract obligating the physician to make in-house referrals whenever possible, according to an article by the Arkansas-based Mitchell

Williams law firm. When physicians are negotiating their employment contract, they can try to get the clause removed.

**Take advantage of exceptions to your referral obligation.** Under the Stark Law, hospitals cannot stop employed physicians from referring outside the system if, in their judgment, it is in the patient’s best medical interests, Mitchell Williams stated.

**Inform patients of your conflict of interest.** Employed physicians should reveal to patients

the organization’s expectation that they should refer patients in-house, says William Andereck, MD, a general internist who is medical director of the medicine and human values program at California Pacific Medical Center in San Francisco.

### 3. REDUCING OPIOID DOSAGES COULD LEAVE PATIENTS SUFFERING

**THE DILEMMA:** In response to the opioid epidemic, state and federal regulators have been set-

ting limits on the opioid dosages that physicians prescribe. But some patients need higher dosages to control their pain, and abruptly lowering dosages can cause painful withdrawal symptoms.

Years ago, the issue was that physicians in general were prescribing too many opioids.

State and federal regulators, however, have recently been issuing rules on the dosages doctors are allowed to prescribe. As of July 2017, 23 states had enacted legislation with some

type of limit, guidance, or requirement related to opioid prescribing, according to one count.

**HOW TO DEAL WITH IT: Consider other therapies besides opioids.** In some cases, Erdek says, physicians can prescribe patients other substances. Examples include anticonvulsants, such as gabapentin; tricyclic medications, such as nortriptyline; and muscle relaxants and anti-inflammatory drugs, he says.

**Go easy on patients with a profound dependence.** “Legacy patients,” those who have been on opioids for years or even decades, can be on very high doses, and “the prospect of going off those meds is terrifying,” Rieder says. “Removing patients from opioids too fast puts them at risk for depression and suicide.”

**Consult with pain specialists.** Primary care physicians (PCPs) have the option of asking pain specialists about opioid dosages and the use of alternative therapies, Erdek says. But PCPs should not try to hand over their opioid patients to pain specialists, because “the pain clinics would be overflowing,” Erdek says.

### 4. WORRY THAT PROVIDING TELEHEALTH SERVICES MIGHT CREATE INFERIOR CARE

**THE DILEMMA:** Telehealth—electronic communication with patients—has been a godsend for patients in remote areas and may take the place of some routine visits, but critics argue that in other cases it may be a poor substitute for face-to-face appointments.

**HOW TO DEAL WITH IT: The alternative may be doing nothing.** When patients run out of their medications and their regular doctor is out of town, using a telehealth service may be the only option, according to David Fleming, MD, an ethicist at the University of Missouri School of Medicine and a member of the Council on Ethical and Judicial Affairs at the AMA. “Telemedicine may be the only solution,” he says.

Medicare, which has long covered telehealth in rural areas, expanded coverage in 2015 to patients with multiple chronic conditions. UnitedHealthcare has expanded coverage options for virtual physician visits for patients in self-funded employer health plans. And Kaiser



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Permanente, the integrated delivery system, now provides more visits virtually than in person.

Guidelines for telehealth can be hard to follow. Goodman contends that the new AMA guidelines are vague at points. For example, the guidelines state, “Although physicians’ fundamental ethical responsibilities do not change, the continuum of possible patient-physician interactions in telehealth/telemedicine give rise to

**Unless you have significant training in genetic testing, consider referring patients to an expert.**

differing levels of accountability for physicians.”

Telehealth is a better fit for some specialties. Fleming notes that PCPs are less likely than specialists to use telehealth. He says this may be because of the expense of setting up a telehealth base for patients to use.

**Consider the need for follow-up care.** Telehealth providers should advise patients “how to arrange for needed care when

follow-up care is indicated,” the current AMA policy states. They should also “encourage users who have primary care physicians to inform their primary physicians about the online health consultation.”

#### 5. GIVING GENETIC TEST RESULTS WHILE BEING UNSURE OF HOW TO INTERPRET RESULTS

**THE DILEMMA:** Genetic testing can help you determine a patient’s predisposition toward a disease, but test results can be hard to interpret and may cause patients unnecessary anxiety.

Genetic tests are becoming ubiquitous. There are 75,000 genetic tests on the market, and 10 new ones enter the market every day, according to a new study. In addition, 97% of insurers cover genetic screening, and Medicare covers affected patients for genetic testing as long as they have a qualifying history.

Some doctors are beginning to routinely order genetic tests. Geisinger Health System recently announced that it will now offer patients DNA sequencing as part of routine preventive care, and Geisinger will pay for the testing.

**HOW TO DEAL WITH IT:** Be able to converse with patients about genetic testing. Many patients expect doctors to talk about genetic testing. Even when patients order DTC tests on their own, many of them want doctors to interpret them.

**Pay close attention to family history.** It’s wise to suggest testing when there is a significant family history of a disease that can be tested for. In a \$4 million malpractice award against a physician, a patient who developed ovarian cancer alleged that her physician should have understood from her family history that she needed to be evaluated.

**Refer patients to an expert.** Unless you have significant training in genetic testing, consider referring patients to an expert in genetic testing, such as an experienced physician or a genetic counselor.

**Be selective about tests for children.** Children whose parents order genetic testing for them have no say over the matter, so it’s important to be selective about ordering tests, says Joel Frader, MD, a pediatrics professor and bioethicist at Northwestern University.

# HIDDEN BOTTLENECKS

SLOWDOWNS CAN BECOME QUICKSAND OVER TIME, SO LOOK FOR THESE PROBLEM AREAS AND FIND OUT HOW TO AVOID THEM

BY LEIGH PAGE

**K**EEPING YOUR WORKFLOW EFFICIENT IS IMPORTANT FOR GOOD PATIENT CARE, AS WELL AS YOUR PRACTICE’S PROFITABILITY AND STAFF’S PEACE OF MIND. Patients won’t have to wait, you won’t feel like you’re on an unending treadmill, and your claims will get paid more quickly.

Practices often run smoothly at first, but bottlenecks can emerge over the years, as more operations and processes are added and team members fall into outdated routines. New technology, extra reporting requirements, and different kinds of patients can change the dynamics.

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To resolve bottlenecks, you need to take a good, hard look at your operations and make some decisive changes. Here are four bottlenecks to look for and some strategies to deal with them:

### 1. AN UNEVEN APPOINTMENT SCHEDULE

You can't keep up with your patient schedule because you have too many same-day appointments, no-shows, and patients with long lists of complaints that will take much longer than the allotted patient visit slot.

#### SOLUTIONS

**Use tactics to reduce no-shows.** When practices expect no-shows, they tend to double-book and overbook appointments, which then cause bottlenecks. In a 2017 Medscape survey, 24% of practices said no-shows made up 11%–20% of all patients.

To reduce no-shows, Linda Girgis, MD, a family physician in South River, New Jersey, recommends calling all patients the day before the appointment to remind them. Other physicians text or email reminders, if they have gathered the patients' online addresses.

**Manage same-day appointments more strategically.** Many patients ask for same-day appointments, which can force the practice to double-book appointments. "This can mean staying late to accommodate all of the patients who show up," Girgis says.

This may entail more careful screening when a patient phones for a same-day appointment. If you don't feel that the patient is critically ill, you can suggest an appointment the following day.

However, if the doctor is not going to screen calls for same-day appointments, the work should be done by registered nurses (RNs) or staff with even more clinical training, such as nurse practitioners, advises the American College of Physicians (ACP). This work "cannot be delegated to unlicensed personnel such as office receptionists," the ACP states. Furthermore, "physicians should be accessible" to RNs doing the screening, and the RNs should use prepared texts to respond to callers' requests, the ACP advises.

**Plan ahead.** At the end of the day, physicians and staff should look at the schedule for the next day. Determine



whether all necessary information is available in the patient's chart the day before. If you don't have all the information, try to get it before the appointment.

**Determine patients' complaints before they meet with the physician.** The goal is to know the patient's full list of complaints in advance. You can then determine which complaints need to be addressed in the current visit and which can be addressed in a future visit.

### 2. EHR DATA ENTRY REQUIREMENTS

Physicians are forced to spend too much time documenting patient information into their EHR and, as a result, are constantly

falling behind with their work and schedule. "This situation is not sustainable," says Marie Brown, MD, an internist and geriatrician at Rush University Medical Center and a physician lead for the American Medical Association's STEPS Forward program. "Doctors are taking their documentation home—and on weekends and even vacation. It's called 'work after work.'"

#### SOLUTIONS

**Make changes in the way you manage your inbox.** For example, EHRs often direct all messages to the doctor's office directly to the physician's inbox as the default destination, Brown says.

Messages that don't need to go to the physician include daily progress notes for hospitalized patients; nurse visit notes for preventive care; routine physical therapy progress notes; test results ordered by consultants; pre-visit labs; and refill requests, according to the module.

**Use nonphysician clinicians to enter information into the EHR.** Physicians get bogged down with EHR work because they think they need to enter all of the information personally. Brown says much of the work can be done by staff. "We wouldn't expect a lawyer who is trying a case to document what is happening in the courtroom," she says. "There's a court

stenographer to do that."

**Consider hiring scribes.** Hiring staff specifically to enter information in the exam room is especially useful for physicians who are poor typists or want to deal more individually with the patient during the visit, says Laurie Morgan, a senior consultant at Capko and Co. in San Francisco.

**Include the patient in the EHR entry process.** Brown says having the patient watch as she enters EHR notes can reduce errors and enhance patients' involvement in their care.

### 3. BACKUP AT THE FRONT DESK

The front desk staff gets overwhelmed with tasks. Receptionists are too busy with other chores to greet patients when they arrive and get their registration started.

#### SOLUTIONS

**Don't make receptionists answer the phone.** When receptionists are assigned to answer the phone, they continually have to decide between the phone and the arriving patient standing before them.

Morgan says that one person can do both jobs in a solo practice, but not in practices of any larger size. "Staff is expected to multi-

task, but it usually means they don't do any of their tasks well," she says. "Assign a different person for each job, and then cross-train them so that they can help each other out in high-volume periods."

**Simplify patient questionnaires.** Brown says patients are often required to fill out the same information again and again. This can lengthen the form-filling process as well as annoy your patients. Review your forms to see whether you've captured key information in a different form.

**Use a patient portal.** Having a portal on your website where patients can fill out forms also helps. "The benefit of having this information in electronic form is that you can add it directly to the chart," Brown says.

### 4. OVERWHELMING VOLUME OF INCOMING PHONE CALLS

Staff is overwhelmed by calls asking to talk to a physician or waiting for medication refills.

#### SOLUTIONS

**Remove the phone from the receptionist's responsibility.** Again, having one person greet patients and answer the phone is an

invitation for bottlenecks to happen. It's more efficient to have one person answer the phone and another person greeting patients.

**Determine why people are calling.** Patients' calls to the practice often involve some aspect of their care process that they are confused about, Brown says. In many cases, patients wouldn't have needed to call if someone had explained the matter and made sure that the patient heard, understood, and remembered what was said.

**Find a better way to handle refills.** In many practices, requests for refills are a major reason for patients to call, and this can significantly tie up the phone.

**Provide a patient portal.** Brown says having a portal has reduced the number of calls her practice receives. A portal can handle many issues, such as requesting appointments, paying bills, and reporting lab results.

**Use phone trees.** Some callers may resent directives to press various numbers for different services, but speaking to a live person is not necessarily a good alternative, Morgan says: "It's a myth that people prefer to talk to a person. The live person is often still going to have to transfer them around."



# MISSING A ‘ZEBRA’: SEE WHAT PHYSICIANS SAY

RARE DISEASES MAY FIRST MASQUERADE AS OTHER CONDITIONS  
BY SANDRA LEVY

**M**edical school teaches physicians that most diagnoses are likely to involve common conditions—and that is what they should be looking for first rather than rare diseases. However, when a physician is faced with a patient with a rare disease, not diagnosing that illness can delay treatment or provide a mistaken diagnosis.

A recent Medscape article about the dangers of missing a “zebra”—misdiagnosing a rare disease—pointed out that juries have awarded millions of dollars in cases involving both primary care physicians and specialists.

The article generated numerous comments from physicians. Many physicians advised their colleagues to listen closely when patients and their families complain that something doesn’t feel right or when they think a diagnosis isn’t correct.

“LISTEN—ALWAYS. REFER IF LESS THAN 100% CERTAIN OF DIAGNOSIS. THE PATIENT HAS ONLY ONE LIFE. WE WILL CONTINUE TO HAVE OTHER PATIENTS. OUR LIFE GOES ON. MAKE SURE OUR EGO DOESN’T POP UP.”

—AN INTERNIST

“I was a fit, active 23-year-old when I developed muscle weakness, numbness and tingling, stiffness, and a sore throat. Multiple doctor visits resulted in shrugs and symptoms blown off, despite the fact that things were getting worse. Fortunately, my father was a pediatric neurologist. Over the phone he asked very specific questions and had me do some specific tasks . . . Three months of hospitalization and months of [occupational therapy] followed. I had Guillain-Barré syndrome. Trust me, I made sure the original doctors knew.”

—A CLINICIAN ON HIS OWN ILLNESS

“Get a specialist on board at the first mention of a symptom. Headache: Get a neurologist; Cough: Get a pulmonologist. Get a nurse practitioner involved as your second opinion . . . It is the patient who has to refuse. Let him take part of the blame if later on it turns out to be a serious condition.”

—AN ENDOCRINOLOGIST

“With insurance carriers denying tests all the time now, it is very difficult to look for zebras. One can recommend a test, but the insurance company denies it because it ‘does not meet criteria.’ A lot a zebras will be missed. Rare diseases are surprisingly common.”

—A PHYSICIAN

“IN MY PRACTICE I WAS CRITICIZED FOR ALWAYS LOOKING FOR ZEBRAS. AS IF THAT TYPE OF THOUGHT PROCESS WAS DEFECTIVE. I WAS SHAMED FOR IT. I CAN TELL YOU THAT I TENDED TO ZEBRAS. AFTER MY OWN CHRONIC HEALTH ISSUES, I THINK THAT ZEBRAS ARE WAY MORE COMMON THAN ANYONE REALIZES, THAT MANY ILLNESSES CONSIDERED RARE ARE NOT RARE AT ALL, JUST MISSED BY ALL THE DOCS WHO ARE LOOKING FOR HORSES.”

—A PEDIATRICIAN

“Nationwide benchmarks have metrics for productivity, which is the 15-minute appointment. I think I do remarkably well within these confines, but at what cost? I am 30% slower than some

—AN INTERNIST

of my colleagues. I often get an hour behind. Patients frequently complain that their appointments don’t start on time, but they often recognize they can’t get this quality of care anywhere else.”

“LOOKING BACK ON A LONG SURGERY CAREER, IT WAS NOT THAT UNUSUAL TO COME ACROSS A RARE CONDITION. BECAUSE THERE ARE A LOT OF THEM OUT THERE. I AM SURE THE SAME THING IS TRUE IN A MEDICAL PRACTICE. PART OF GOOD TRAINING IS TO RECOGNIZE THAT YOU ARE NOT LOOKING AT A HORSE AND TO START THINKING OF THE ZEBRAS.”

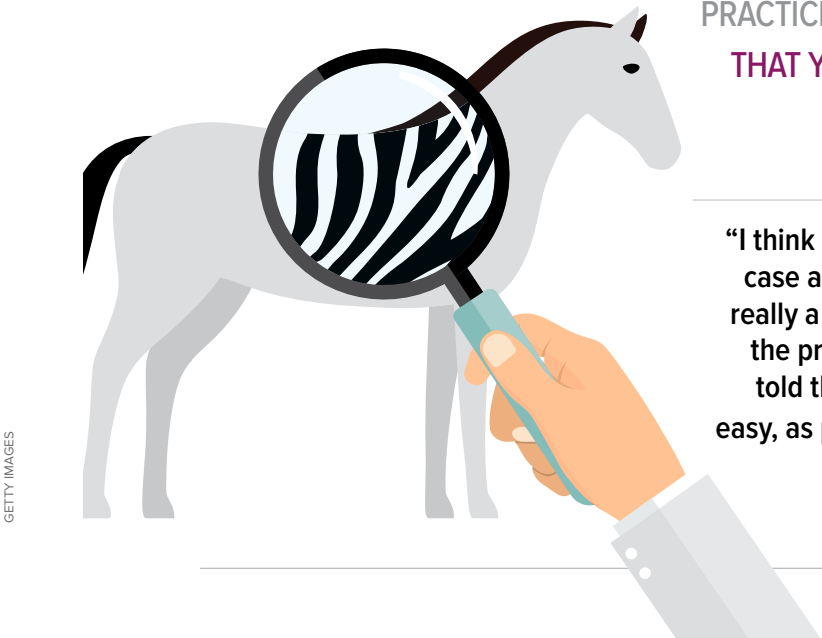
—A SURGEON

“I think it’s not about ruling out all the possible zebras on every case as much as it is about making sure your striped animal is really a horse. I’ve seen several cases of misdiagnosis in which the primary on the case simply labeled them as ‘atypical’ and told them sometimes people fail to respond to treatment. It’s easy, as physicians, to forget that the diagnosis of ‘atypical’ anything should be a diagnosis of exclusion.”

—A PHYSICIAN

“OUR CURRENT MEDICAL SYSTEM PENALIZES USING YOUR BRAIN AND DEVOTING TIME TO REALLY INTERACT WITH A PATIENT. THESE ACTIVITIES ARE NOT AT ALL REWARDED, AND MOST PRACTICING PHYSICIANS NEED TO MAKE AT LEAST SOME MONEY TO SURVIVE AND PAY THE OVERHEAD. ADMINISTRATORS, EVEN THOUGH (THEY) PAY LIP SERVICE TO ‘QUALITY’ AND ‘VALUE-CARE,’ ONLY PAY ATTENTION TO VOLUME AND [RELATIVE-VALUE UNITS]. HOW CAN YOU PRACTICE QUALITY MEDICINE IF YOU’RE BEING ASKED TO SEE PATIENTS EVERY 15 MINUTES OR LESS?”

—A RHEUMATOLOGIST



GETTY IMAGES

DR ERIC TOPOL AND DR JOHN P. A. IOANNIDIS  
MOST RESEARCH  
IS FLAWED; LET'S FIX IT

ERIC J. TOPOL, MD, editor-in-chief of Medscape, speaks with JOHN P. A. IOANNIDIS, MD, DSc, professor of medicine and of health research and policy at Stanford University School of Medicine and a professor of statistics at Stanford University School of Humanities and Sciences, about bias and accuracy in medical research.



ERIC TOPOL, MD



JOHN P. A. IOANNIDIS,  
MD, DSc

There is no reason  
why we should  
continue to live with  
suboptimal evidence.

➤ **DR TOPOL:** You are the “contrarian of medicine.” You seem like you were made for this role you have, in terms of the conscience of biomedicine. How did you get your roots in this model that you really espouse?

➤ **DR IOANNIDIS:** I loved lots of different aspects of the scientific method and scientific discipline I found in mathematics, biology, bench research, clinical research, and clinical epidemiology. I realized that I was making errors again and again in almost everything that I was trying. I started realizing that other people were also making errors—in the lab, the clinic, and in published literature. Errors are common. They are human. Some of them are probably more common than they should be.

**DR TOPOL:** The problem we have in medicine, though, is this evidence basis, which as you have really proven over the years is so shaky and tenuous. We are trying to make

decisions for patients and select treatments and tests and whatnot. What are we going to do since most of the evidence is baseless?

**DR IOANNIDIS:** Some evidence is reliable. There is a gradient. We have strong evidence for some treatments, interventions, and policies, and we need to do something because of it.

This is not just for interventions but for risk factors. Even in observational epidemiology, no one would deny that smoking is horrible and is going to kill 1 billion people unless we get rid of it. We don’t need randomized trials to prove that.

But, of course, there is the other end of the gradient, where there is a lot of unreliable evidence. A lot of evidence is very tenuous. We need to train people to understand what the limitations are, what the caveats are, how much they can trust or distrust what they read or what they see, and what they are being called to do. Then make them ask for better evidence.

There is no reason why we should continue to live

with suboptimal evidence. Clinicians and clinical researchers should be at the forefront because they realize on a daily basis that they don’t have evidence they can trust. They can create questions to try to get the type of evidence they need.

**DR TOPOL:** This brings up something that just happened. One area that you have tackled is nutritional science. The Mediterranean diet was studied in PREDIMED, the largest trial of a randomized diet using hard outcomes. It was published in 2013 in the *New England Journal of Medicine*, and now *NEJM* retracted it and republished it in the same day. It had all sorts of irregularities. What is your take on this? It is right up your alley as to flawed science.

**DR IOANNIDIS:** Nutrition is clearly a mess, and I have long advocated that we can fix some of that mess by running large-scale, long-term, randomized trials with clinical endpoints. PREDIMED was a trial that tried to do that.

But unfortunately, PREDIMED seemed to take the path of observational epidemiology in publishing zillions of papers with results that were far more tenuous, and I think what we saw in the retraction was a signal that the data had major flaws. Clearly, the retraction was the right thing to do.

I think that the problem that was detected by statistical analysis was with baseline characteristics being so similar. The correction that led to the re-publication does not explain that this cannot happen by chance; meaning, there is no reason

why (if indeed a whole village was randomized as an entity instead of on an individual basis, or some couples were randomized together rather than as individuals) that should not have led to the pattern that was detected by testing the baseline characteristics.

**DR TOPOL:** You have emphasized in some of your writings the intellectual conflict of interest. I think that is important. For the most part, people don’t really understand bias and the fact that so many careers are tagged to a particular belief system and pursuit. One critique of that is, “John’s

role is to be the take-down artist and that is an intellectual conflict.” How do you respond to that charge?

**DR IOANNIDIS:** Yes, I think that I am biased. I think this is unavoidable and people should take that for granted when they read my work and then when they read other scientists’ work. We all have some priors, and sometimes it is possible to track these priors based on what we have published.

I don’t think it is wrong to have opinions or hypotheses. I don’t think it is wrong even to have beliefs. To be honest, when

I launch a new project, I try to be as open as possible to all types of outcomes. If anything, my biases are more towards getting non-significant results. If I get significant results, even if it is without biases, I have to ask myself, “Why did I get that?” Sometimes, I have found errors in the process, hopefully early enough before publishing.

What makes a scientist is an acknowledgement that he or she can be biased. We have to watch out for that possibility in whatever we do.

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## THE JEOPARDY OF A STATE MEDICAL BOARD INVESTIGATION

BY MARK CRANE

**P**hysicians often worry that a malpractice suit could derail their career and financial livelihood. Yet another potential source of worry is the jeopardy that physicians face from a complaint filed with a state medical board.

Any patient, colleague, pharmacist, or hospital can file a complaint at any time. No matter how frivolous you may regard the allegation, the boards are required to begin at least a preliminary investigation. In some states, your accuser can remain anonymous, at least initially, and you may never even see the complaint. Unlike a criminal matter or civil case, you may not have the right to face your accuser. Although, if the case progresses, the identity of the complainant is usually revealed or physicians are able to figure it out.

An investigation into a blatantly false accusation or relatively minor matter such as alleged rudeness to a patient can morph into a full-scale probe of every aspect of your practice. Boards have the right to expand investigations way

beyond the initial complaint, such as demanding to see every medical record in your office. While that isn't typical, attorneys say it happens occasionally. On the other hand, a large percentage of investigations are without merit and are closed before the physician is even informed of the complaint.

Some state boards have taken an almost zero-tolerance approach to complaints, both serious and minor, say attorneys who defend physicians. "The boards naturally want to protect the public

from doctors they consider unsafe or impaired," says Brian H. Tew, MD, JD, an attorney in Houston. "Some physicians are scoundrels who deserve whatever they get. But the vast majority aren't a danger to the public, although they may have made mistakes. The pendulum has swung too far. Boards are fining doctors a lot of money and issuing reprimands and suspensions more than ever before. I haven't seen any metric to show that medicine has improved because of their aggressive stance."

ALISON SEIFER

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“The boards are more aggressive now,” says Ronald W. Chapman Sr, an attorney with offices in Florida and Michigan. “Boards have to protect the public. But sometimes they operate from an ivory tower, not the practice of medicine in the real world. You can’t always have a perfect record. The boards can put unrealistic pressures on physicians for some pretty minor stuff.”

Here are some dangers to avoid and key areas state board investigators are looking into.

**HAVE AN ATTORNEY** “The Ohio Board of Medicine receives about 9,000 complaints a year,” notes Beth Collis, an attorney in Columbus. “Many are minor or frivolous, such as allegations that the doctor or his staff was rude to the patient or family, billing questions, being forced to wait too long for an appointment, etc. The board generally doesn’t take action in these cases and may not even inform the doctor of them.

“In one case, the physician terminated a patient from his practice who was non-compliant and a drug-seeker,” she says. “But the doctor used foul language and the patient complained. The board looked into it and found for the doctor but warned him about being disrespectful.”

Some physicians simply decline to answer the complaint. That’s a big mistake. Failing to respond to a complaint can be grounds

for disciplinary action. “You can’t just blow off a board investigation,” Collis says. “You must cooperate.”

David L. Adelson, an attorney with Norris, McLaughlin & Marcus in Bridgewater, New Jersey, agrees. “Boards may demand records of other patients who’ve had the same procedure. Health care attorneys can proactively address issues before the board demands it, attempt to limit the scope of the investigation, and help doctors find witnesses to testify for them.”

“Administrative law is a specialty, so don’t hire a divorce or real estate lawyer. The rules are different,” Tew says. “One doctor intended to write back to the board before consulting an attorney. I was glad I could stop him. The letter was self-serving and he threatened to sue the board for emotional damages they’d caused him. That certainly wouldn’t have helped his case. Doctors might react out of anger. An attorney will prevent that.”

**PRESCRIBING AND DOCUMENTATION GETS BOARD ATTENTION** State boards have focused intensely on the opioid epidemic and often work hand in hand with the Drug Enforcement Agency when investigating physicians.

Any hint of overprescribing is likely to spur the board’s interest. “The board is checking doctors’ records to see if there is a medical necessity for the kind and

amount of drug prescribed. Not having thorough records makes the case hard to defend,” Chapman says.

“You have to medically justify what you did, and records are essential. Many doctors are too lax, too willing to believe a patient who ‘lost’ his prescription.

All states have databases physicians must check to track a patient’s drug prescription history. If you can’t prove that you checked the database, state boards will act, and the lack of documentation makes for a weak defense.

In Ohio, the state system shows all controlled substances taken by a patient. “Is the patient getting drugs from other doctors? The board wants to see copies of the report or at least documentation that the prescribing doctor reviewed them,” Collis says. “If the doctor doesn’t describe the reason for prescribing opioids, he can even be charged criminally for trafficking in drugs. It can’t be more serious.”

### DON’T AVOID THE PATIENT

The main trigger for a complaint is a dissatisfied patient, Chapman says. “Doctors must deal with the patient’s frustration. Bedside manner counts for a lot. Some physicians avoid patients after a poor outcome. That just makes the patient think you must be hiding something. It’s always worth the time to sit down with the patient

and family to air out the issue.”

If you know that a patient is unhappy with the outcome or progress of a treatment, don’t avoid him. Those are the patients who may be likely to complain to a state board. Be sure to have a mechanism for patient feedback in your office, whether it’s a complaint through the patient portal or a suggestion box, etc.

It’s best to speak with the patient directly, Chapman says. You can acknowledge that the treatment didn’t achieve the results you both wanted and encourage questions about future care.

The vast majority of complaints filed against doctors are dismissed without any discipline such as a reprimand or



suspension of the license. Still, the stakes are high, and physicians can avoid problems by being candid with patients and taking any complaint seriously.



**BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.**

#### 1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of: **Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR) in Patients with DME**

#### 4 CONTRAINDICATIONS

##### 4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

##### 4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

##### 4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

#### 5 WARNINGS AND PRECAUTIONS

**5.1 Endophthalmitis and Retinal Detachments.** Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (see *Adverse Reactions* (6.1)). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (see *Dosage and Administration* (2.7) and *Patient Counseling Information* (17)).

**5.2 Increase in Intraocular Pressure.** Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (see *Adverse Reactions* (6.1)). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (see *Dosage and Administration* (2.7)).

**5.3 Thromboembolic Events.** There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.6% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (6 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

#### 6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity (see *Contraindications* (4.3))
- Endophthalmitis and retinal detachments (see *Warnings and Precautions* (5.1))
- Increase in intraocular pressure (see *Warnings and Precautions* (5.2))
- Thromboembolic events (see *Warnings and Precautions* (5.3))

**6.1 Clinical Trials Experience.** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

**Neovascular (Wet) Age-Related Macular Degeneration (AMD).** The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

**Macular Edema Following Retinal Vein Occlusion (RVO).** The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

**Diabetic Macular Edema (DME).** The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

**6.2 Immunogenicity.** As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

##### Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose (see *Animal Data*).

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept (see *Clinical Pharmacology* (12.1)), treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population 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 15-20%, respectively.

##### Data

##### Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternabrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

##### 8.2 Lactation

##### Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

##### 8.3 Females and Males of Reproductive Potential

##### Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

##### Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment (see *Nonclinical Toxicology* (13.1)).

**8.4 Pediatric Use.** The safety and effectiveness of EYLEA in pediatric patients have not been established.

**8.5 Geriatric Use.** In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

#### 17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (see *Warnings and Precautions* (5.1)).

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (see *Adverse Reactions* (6)). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:  
**Regeneron Pharmaceuticals, Inc.**  
777 Old Saw Mill River Road  
Tarrytown, NY 10591

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Issue Date: June 2017  
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

**REGENERON**



# POWER TO PREVAIL

As demonstrated in phase 3 clinical trials evaluating BCVA,\* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS<sup>†</sup> in DR in Patients with DME,<sup>†</sup> as well as your clinical experience

Start with EYLEA for proven efficacy outcomes<sup>1</sup>



AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema;  
DR = Diabetic Retinopathy; RVO = Retinal Vein Occlusion.

Dosing driving efficacy outcomes across all indications.<sup>1</sup>  
Learn more at [EYLEA.us/dose](http://EYLEA.us/dose)

## INDICATIONS AND IMPORTANT SAFETY INFORMATION

### INDICATIONS

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with:

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

### CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

### WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

Please see adjacent Brief Summary.

\*Best-corrected visual acuity.

<sup>†</sup>Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

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 **EYLEA®**  
(aflibercept) Injection  
For Intravitreal Injection

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

### ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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