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ONLINE EXCLUSIVE

Would your patient benefit from a monoclonal antibody?

These unique agents may be the answer when other treatments fail or are intolerable for patients with asthma, atopic dermatitis, hyperlipidemia, osteoporosis, or migraine headaches.

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PRACTICE RECOMMENDATIONS

› *Consider anti-immunoglobulin E, anti-interleukin 5, or anti-interleukin 4/interleukin 13 for patients with moderate-to-severe asthma and type 2 airway inflammation.* (B)

› *Consider dupilumab for patients with moderate-to-severe atopic dermatitis (with or without topical corticosteroids), or when traditional oral therapies are inadequate or contraindicated.* (B)

› *Consider proprotein convertase subtilisin/kexin type 9 inhibitors for patients with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease when maximally tolerated statins or ezetimibe have not lowered low-density lipoprotein cholesterol levels far enough.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Small-molecule drugs such as aspirin, albuterol, atorvastatin, and lisinopril are the backbone of disease management in family medicine.[1] However, large-molecule biological drugs such as monoclonal antibodies (MAbs) are increasingly prescribed to treat common conditions. In the past decade, MAbs comprised 20% of all drug approvals by the US Food and Drug Administration (FDA), and today they represent more than half of drugs currently in development.[2] Fifteen MAbs have been approved by the FDA over the past decade for asthma, atopic dermatitis (AD), hyperlipidemia, osteoporosis, and migraine prevention.[3] This review details what makes MAbs unique and what you should know about them.

The uniqueness of monoclonal antibodies

MAbs are biologics, but not all biologics are MAbs—eg, adalimumab (Humira) is a MAb, but etanercept (Enbrel) is not. MAbs are therapeutic proteins made possible by hybridoma technology used to create an antibody with single specificity.[4-6] Monoclonal antibodies differ from small-molecule drugs in structure, dosing, route of administration, manufacturing, metabolism, drug interactions, and elimination (**TABLE 1**[7-9]).

MAbs can be classified as *naked*, "without any drug or radioactive material attached to them," or *conjugated*, "joined to a chemotherapy drug, radioactive isotope, or toxin."[10] MAbs work in several ways, including competitively inhibiting ligand-receptor binding, receptor blockade, or cell elimination from indirect immune system activities such as antibody-dependent cell-mediated cytotoxicity.[11,12]

Monoclonal antibody uses in family medicine

Asthma

Several MAbs have been approved for use in severe asthma, including but not limited to: omalizumab (Xolair),[13] mepolizumab

TABLE 1

Comparing small-molecule drugs and biologics used to treat asthma

Features	Fluticasone propionate HFA (Flovent)[7,8]	Mepolizumab (Nucala)[9]
Adult dosing/ administration	88 µg inhaled bid	100 mg subcutaneously every 4 weeks
Indication	Maintenance treatment of asthma as prophylactic therapy in patients ≥ 4 y	Add-on maintenance treatment for severe asthma in patients ≥ 6 y with an eosinophilic phenotype
Adverse reactions (> 5%)	Upper respiratory tract infection (18%), throat irritation (8%), sinusitis/sinus infection (6%), headache (11%)	Headache (19%), injection site reactions (8%), back pain (5%), fatigue (5%)
Bioavailability	< 1%	80%
Metabolism	Cytochrome P450 3A4	Degraded by proteolytic enzymes widely distributed around the body and not restricted to hepatic tissue
Excretion	Mainly fecal; < 5% urine	N/A
Half-life	7.8 h	16 to 22 d
Target	Influences mast cells, eosinophils, macrophages, lymphocytes, histamine, eicosanoids, leukotrienes, and cytokines to reduce inflammation	Inhibits interleukin-5 and thereby blocks the growth, differentiation, recruitment, activation, and survival of eosinophils that play a role in inflammation
Drug-drug interactions	Use not recommended with strong cytochrome P450 3A4 inhibitors (eg, ritonavir, ketoconazole)	No evidence of interactions with commonly co-administered small-molecule drugs
Immunogenicity	N/A	6% had anti-mepolizumab antibodies, which can increase mepolizumab clearance by 20%

N/A, not available.

(Nucala),[9,14] and dupilumab (Dupixent).[15] All 3 agents can be self-administered subcutaneously (SC), depending on the clinician's assessment. The Global Initiative for Asthma (GINA) guidelines recommend that, prior to considering MAb therapy for a patient who has asthma, clinicians should assess the patient's inhaler technique and adherence, treat comorbidities such as gastroesophageal reflux disease, and modify triggering factors such as smoking or allergen exposure.[16] In patients with severe asthma still uncontrolled after receiving high-dose inhaled corticosteroids (ICSs) or the lowest possible dose of oral corticosteroid (OCS), GINA recommends assessing for type 2 airway inflammation: blood eosinophils ≥ 150/µL, sputum eosinophils ≥ 2%, or evidence of allergen stimulation.[16] If these factors are present, consider prescribing anti-immunoglobulin E (anti-IgE) (omalizumab), anti-interleukin-5 (anti-IL-5) (mepolizumab), or anti-IL-4/anti-IL-13 (dupilumab).[16]

Omalizumab is a humanized MAb that prevents IgE antibodies from binding to mast cells and basophils, thereby reducing inflammatory mediators.[13] A systematic review found that, compared with placebo, omalizumab used in patients with inadequately controlled moderate-to-severe asthma led to significantly fewer asthma exacerbations (absolute risk reduction [ARR], 16% vs 26%; odds ratio [OR] = 0.55; 95% CI, 0.42-0.60; number needed to treat [NNT] = 10) and fewer hospitalizations (ARR, 0.5% vs 3%; OR = 0.16; 95% CI, 0.06-0.42; NNT = 40).[13]

Significantly more patients in the omalizumab group were able to withdraw from, or reduce, the dose of ICS. GINA recommends

omalizumab for patients with positive skin sensitization, total serum IgE ≥ 30 IU/mL, weight within 30 kg to 150 kg, history of childhood asthma and recent exacerbations, and blood eosinophils ≥ 260/mcL.[16] Omalizumab is also approved for use in chronic spontaneous urticaria and nasal polyps.

Mepolizumab is a humanized MAb that inhibits IL-5, effectively blocking the growth, differentiation, recruitment, activation, and survival of eosinophils.[14] Mepolizumab was studied in patients with frequent exacerbations while already taking high-dose ICSs. The mean rate of clinically consequential exacerbations was significantly reduced with mepolizumab compared with placebo (0.83 vs 1.74; $P < .001$).[17] This translates to about 1 less moderate-to-severe asthma exacerbation per year per person.

Another trial found that mepolizumab reduced total OCS doses in patients with severe asthma by 50% without increasing exacerbations or worsening asthma control.[18] All 3 anti-IL-5 drugs—including not only mepolizumab, but also benralizumab (Fasenra) and reslizumab (Cinqair)—appear to yield similar improvements. A 2017 systematic review found all anti-IL-5 treatments reduced rates of clinically significant asthma exacerbations (treatment with OCS for ≥ 3 days) by roughly 50% in patients with severe eosinophilic asthma and a history of ≥ 2 exacerbations in the past year.[14] Mepolizumab, according to GINA, is preferred for patients with blood eosinophils ≥ 300/μL and severe exacerbations, nasal polyposis, adult-onset asthma, and maintenance OCS at baseline.[16] Mepolizumab is also approved for use in eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and rhinosinusitis with nasal polyps.

Dupilumab is a humanized MAb that inhibits IL-4 and IL-13, which influence multiple cell types involved in inflammation (eg, mast cells, eosinophils) and inflammatory mediators (histamine, leukotrienes, cytokines).[15] In a recent study of patients with uncontrolled asthma, dupilumab 200 mg every 2 weeks compared with placebo showed a modest reduction in the annualized rate of severe asthma exacerbations (0.46 exacerbations vs 0.87, respectively). Dupilumab was effective in patients with blood eosinophil counts ≥ 150/μL but was ineffective in patients with eosinophil counts < 150/μL.[15]

For patients ≥ 12 years old with severe eosinophilic asthma, GINA recommends using dupilumab as add-on therapy for an initial trial of 4 months at doses of 200 or 300 mg SC every 2 weeks, with preference for 300 mg SC every 2 weeks for OCS-dependent asthma. Dupilumab is approved for use in AD and chronic rhinosinusitis with nasal polyposis. If a biologic agent is not successful after a 4-month trial, consider a 6- to 12-month trial. If efficacy is still minimal, consider switching to an alternative biologic therapy approved for asthma.[16]

ASTHMA: Test your skills

Subjective findings: A 19-year-old man presents to your clinic. He has a history of nasal polyps and allergic asthma. At age 18, he was given a diagnosis of severe persistent asthma. He has shortness of breath during waking hours 4 times per week, and treats each of these episodes with albuterol. He also wakes up about twice a week with shortness of breath and has some limitations in normal activities. He reports missing his prescribed fluticasone/salmeterol 500/50 μg, 1 inhalation bid, only once each month. In the last year, he has had 2 exacerbations requiring oral steroids.

Medications: Albuterol 90 μg, 1-2 inhalations, q6h prn; fluticasone/salmeterol 500/50 μg, 1 inhalation bid; tiotropium 1.25 μg, 2 puffs/d; montelukast 10 mg every morning; prednisone 10 mg/d.

Objective data: Patient is in no apparent distress and afebrile, and oxygen saturation on room air is 97%. Ht, 70 inches; wt, 75 kg. Labs: IgE, 15 IU/mL; serum eosinophils, 315/μL.

Which MAb would be appropriate for this patient? Given that the patient has a blood eosinophil level ≥ 300/μL and severe exacerbations, adult-onset asthma, nasal polyposis, and maintenance OCS at baseline, it would be reasonable to initiate mepolizumab 100 mg SC every 4 weeks, or dupilumab

Before considering a monoclonal antibody for asthma, assess the patient's inhaler technique and adherence, treat comorbidities, and modify triggering factors.

600 mg once, then 300 mg SC every 2 weeks. Both agents can be self-administered.

Atopic dermatitis

Two MAbs—dupilumab and tralokinumab (Adbry; inhibits IL-13)—are approved for treatment of AD in adults that is uncontrolled with conventional therapy.[15,19] Dupilumab is also approved for children ≥ 6 months old.[20] Both MAbs are dosed at 600 mg SC, followed by 300 mg every 2 weeks. Dupilumab was compared with placebo in adult patients who had moderate-to-severe AD inadequately controlled on topical corticosteroids (TCSs), to determine the proportion of patients in each group achieving improvement of either 0 or 1 points or ≥ 2 points in the 5-point Investigator Global Assessment (IGA) score from baseline to 16 weeks.[21] Thirty-seven percent of patients receiving dupilumab 300 mg SC weekly and 38% of patients receiving dupilumab 300 mg SC every 2 weeks achieved the primary outcome, compared with 10% of those receiving placebo ($P < .001$).[21] Similar IGA scores were reported when dupilumab was combined with TCS, compared with placebo.[22]

In atopic dermatitis, MAbs, unlike other systemic agents, do not require frequent monitoring of factors such as blood pressure and kidney or liver function.

It would be reasonable to consider dupilumab or tralokinumab in patients with: cutaneous atrophy or hypothalamic-pituitary-adrenal axis suppression with TCS, concerns of malignancy with topical calcineurin inhibitors, or problems with the alternative systemic therapies (cyclosporine-induced hypertension, nephrotoxicity, or immunosuppression; azathioprine-induced malignancy; or methotrexate-induced bone marrow suppression, renal impairment, hepatotoxicity, pneumonitis, or gastrointestinal toxicity).[23]

A distinct advantage of MAbs over other systemic agents in the management of AD is that MAbs do not require frequent monitoring of blood pressure, renal or liver function, complete blood count with differential, electrolytes, or uric acid. Additionally, MAbs have fewer black box warnings and adverse reactions when compared with other systemic agents. For dupilumab, the main adverse reactions (that occurred with > 10% frequency in trials) were injection site reactions and upper respiratory tract infections.[15] Antidrug antibody development occurred in 4.2%.[15] Tralokinumab had > 20% incidence of upper respiratory tract infections.[19]

Hyperlipidemia

Three MAbs are approved for use in hyperlipidemia: the angiopoietin-like protein 3 (ANGPTL3) inhibitor evinacumab (Evkeeza)[24] and 2 proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, evolocumab (Repatha)[25] and alirocumab (Praluent).[26]

ANGPTL3 inhibitors block ANGPTL3 and reduce endothelial lipase and lipoprotein lipase activity, which in turn decreases low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride formation. PCSK9 inhibitors prevent PCSK9 from binding to LDL receptors, thereby maintaining the number of active LDL receptors and increasing LDL-C removal.

Evinacumab is indicated for homozygous familial hypercholesterolemia and is administered intravenously every 4 weeks. Evinacumab has not been evaluated for effects on cardiovascular morbidity and mortality.

Evolocumab 140 mg SC every 2 weeks or 420 mg SC monthly has been studied in patients on statin therapy with LDL-C ≥ 70 mg/dL. Patients on evolocumab experienced significantly less of the composite endpoint of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina, or coronary revascularization compared with placebo (9.8% vs 11.3%; hazard ratio [HR] = 0.85; 95% CI, 0.79-0.92; NNT = 67.[27]

Alirocumab 75 mg SC every 2 weeks has also been studied in patients receiving statin therapy with LDL-C ≥ 70 mg/dL. Patients taking alirocumab experienced significantly less of the composite endpoint of death from coronary heart disease, nonfatal MI, ischemic stroke, or hospitalization for unstable angina compared with placebo (9.5% vs 11.1%; HR = 0.85; 95% CI, 0.78-0.93; NNT = 63).[28]

According to the 2018 AHA Cholesterol Guidelines, PCSK9 inhibitors are indicated for patients receiving maximally tolerated LDL-C-lowering therapy (statin and ezetimibe) with LDL-C ≥ 70 mg/dL, if they have

had multiple atherosclerotic cardiovascular disease (ASCVD) events or 1 major ASCVD event with multiple high-risk conditions (eg, heterozygous familial hypercholesterolemia, history of coronary artery bypass grafting or percutaneous coronary intervention, hypertension, estimated glomerular filtration rate of 15 to 59 mL/min/1.73m^2).[29] For patients without prior ASCVD events or high-risk conditions who are receiving maximally tolerated LDL-C-lowering therapy (statin and ezetimibe), PCSK9 inhibitors are indicated if the LDL-C remains ≥ 100 mg/dL.

Osteoporosis

The 2 MAbs approved for use in osteoporosis are the receptor activator of nuclear factor κB ligand (RANKL) inhibitor denosumab (Prolia)[30] and the sclerostin inhibitor romosozumab (Evenity).[31]

Denosumab prevents RANKL from binding to the RANK receptor, thereby inhibiting osteoclast formation and decreasing bone resorption. Denosumab is approved for use in women and men who are at high risk of osteoporotic fracture, including those taking OCSs, men receiving androgen deprivation therapy for prostate cancer, and women receiving adjuvant aromatase inhibitor therapy for breast cancer.

In a 3-year randomized trial, denosumab 60 mg SC every 6 months was compared with placebo in postmenopausal women with T-scores < –2.5, but not < –4.0 at the lumbar spine or total hip. Denosumab significantly reduced new radiographic vertebral fractures (2.3% vs 7.2%; risk ratio [RR] = 0.32; 95% CI, 0.26-0.41; NNT = 21), hip fracture (0.7% vs 1.2%), and nonvertebral fracture (6.5% vs 8.0%).[32] Denosumab carries an increased risk of multiple vertebral fractures following discontinuation, skin infections, dermatologic reactions, and severe bone, joint, and muscle pain.

Romosozumab inhibits sclerostin, thereby increasing bone formation and, to a lesser degree, decreasing bone resorption. Romosozumab is approved for use in postmenopausal women at high risk for fracture (ie, those with a history of osteoporotic fracture or multiple risk factors for fracture) or in patients who have not benefited from or are intolerant of other therapies. In one study, postmenopausal women with a T-score of –2.5 to –3.5 at the total hip or femoral neck were randomly assigned to receive either romosozumab 210 mg SC or placebo for 12 months, then each group was switched to denosumab 60 mg SC for 12 months. After the first year, prior to initiating denosumab, patients taking romosozumab experienced significantly fewer new vertebral fractures than patients taking placebo (0.5% vs 1.8%; RR = 0.27; 95% CI, 0.16-0.47; NNT = 77); however, there was no significant difference between the 2 groups with nonvertebral fractures (HR = 0.75; 95% CI, 0.53-1.05).[33]

In another study, romosozumab 210 mg SC was compared with alendronate 70 mg weekly, followed by alendronate 70 mg weekly in both groups. Over the first 12 months, patients treated with romosozumab saw a significant reduction in the incidence of new vertebral fractures (4% vs 6.3%; RR = 0.63, $P < .003$; NNT = 44). Patients treated with romosozumab with alendronate added for another 12 months also saw a significant reduction in new incidence of vertebral fractures (6.2% vs 11.9%; RR = 0.52; $P < .001$; NNT = 18).[34] There was a higher risk of cardiovascular events among patients receiving romosozumab compared with those treated with alendronate, so romosozumab should not be used in individuals who have had an MI or stroke within the previous year.[34] Denosumab and romosozumab offer an advantage over some bisphosphonates in that they require less frequent dosing and can be used in patients with renal impairment (creatinine clearance < 35 mL/min, in which zoledronic acid is contraindicated and alendronate is not recommended; < 30 mL/min, in which risedronate and ibandronate are not recommended).

Migraine prevention

Four calcitonin gene-related peptide (CGRP) antagonists have been approved for migraine prevention: erenumab (Aimovig),[35] eptinezumab (Vyepti),[36] fremanezumab (Ajovy),[37] and galcanezumab (Emgality).[38] CGRP is released at areas in and around the brain, causing vasodilation and inflammation that is thought to be the major causative factor for migraine headaches.[39]

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Erenumab, fremanezumab, and galcanezumab are all available in subcutaneous autoinjectors (or syringe with fremanezumab). Eptinezumab is an intravenous (IV) infusion given every 3 months.

Erenumab is available in both 70-mg and 140-mg dosing options. Fremanezumab can be given as 225 mg monthly or 675 mg quarterly. Galcanezumab has an initial loading dose of 240 mg followed by 120 mg given monthly. Erenumab targets the CGRP receptor; the others target the CGRP ligand. Eptinezumab has 100% bioavailability and reaches maximum serum concentration sooner than the other antagonists (due to its route of administration), but it must be given in an infusion center. Few insurers approve the use of eptinezumab unless a trial of least 1 of the monthly injectables has failed.

There are no head-to-head studies of the medications in this class. Additionally, differing study designs, definitions, statistical analyses, endpoints, and responder-rate calculations make it challenging to compare them directly against one another. At the very least, all of the CGRP MAbs have efficacy comparable to conventional preventive migraine medications such as propranolol, amitriptyline, and topiramate.[40]

The most commonly reported adverse effect for all 4 CGRPs is injection site reaction, which was highest with the quarterly fremanezumab dose (45%).[37] Constipation was most notable with the 140-mg dose of erenumab (3%)[35]; with the other CGRP MAbs it is comparable to that seen with placebo (< 1%).

Erenumab-induced hypertension has been identified in 61 cases reported through the FDA Adverse Event Reporting System (FAERS) as of 2021.[41] This was not reported during MAb development programs, nor was it noted during clinical trials. Blood pressure elevation was seen within 1 week of injection in nearly 50% of the cases, and nearly one-third had pre-existing hypertension.[41] Due to these findings, the erenumab prescribing information was updated to include hypertension in its warnings and precautions. It is possible that hypertension could be a class effect, although trial data and posthoc studies have yet to bear that out. Since erenumab was the first CGRP antagonist brought to market (May 2018 vs September 2018 for fremanezumab and galcanezumab), it may have accumulated more FAERS reports. Nearly all studies exclude patients with older age, uncontrolled hypertension, and unstable cardiovascular disease, which could impact data.[41]

Overall, this class of medications is very well tolerated, easy to use (again, excluding eptinezumab), and maintains a low adverse effect profile, giving added value compared with conventional preventive migraine medications.

The American Headache Society recommends a preventive oral therapy for at least 3 months before trying an alternative medication. After treatment failure with at least 2 oral agents, CGRP MAbs are recommended.[42] CGRP antagonists offer convenient dosing, bypass gastrointestinal metabolism (which is useful in patients with nausea/vomiting), and have fewer adverse effects than traditional oral medications.

Worth noting. Several newer oral agents have been recently approved for migraine prevention, including atogepant (Qulipta) and rimegepant (Nurtec), which are also CGRP antagonists. Rimegepant is approved for both acute migraine treatment and prevention.

MIGRAINE: Test your skills

Subjective findings: A 25-year-old woman presents to your clinic for management of episodic migraines with aura. Her baseline average migraine frequency is 9 headache days/month. Her migraines are becoming more frequent despite treatment. She fears IV medication use and avoids hospitals.

History: Hypertension, irritable bowel syndrome with constipation (IBS-C), and depression. The patient is not pregnant or trying to get pregnant.

Medications: Current medications (for previous 4 months) include propranolol 40 mg at bedtime, linaclotide 145 µg/d, citalopram 20 mg/d, and sumatriptan 50 mg prn. Past medications include venlafaxine 150 mg po bid for 5 months.

TABLE 2

Average wholesale prices of MAbs[45]

Generic name (brand)	Indication	Typical dosing	Monthly cost
Dupilumab (Dupixent)	Asthma, atopic dermatitis	300 mg every other wk	$1998.92
Mepolizumab (Nucala)	Asthma	100 mg every 4 wks	$3857.39
Omalizumab (Xolair)	Asthma	300 mg every other wk	$5746.60
Tralokinumab (Adbry)	Atopic dermatitis	300 mg every other wk	$4018.56
Alirocumab (Praluent)	Hyperlipidemia	150 mg every other wk	$540.00
Evinacumab (Evkeeza)	Hyperlipidemia	1200 mg/mo[a]	$5850.00
Evolocumab (Repatha)	Hyperlipidemia	420 mg/mo	$187.45
Denosumab (Prolia)	Osteoporosis	60 mg every 6 mo	$286.83
Romosozumab (Evenity)	Osteoporosis	210 mg/mo	$2099.18
Eptinezumab (Vyepti)	Migraine prevention	100 mg every 3 mo	$628.27
Erenumab (Aimovig)	Migraine prevention	70 mg/mo	$811.75
Fremanezumab (Ajovy)	Migraine prevention	225 mg/mo	$532.00
Galcanezumab (Emgality)	Migraine prevention	120 mg/mo	$783.36

MAbs, monoclonal antibodies.
Average wholesale price is provided as a reference only.
[a] Average US adult body weight is 82 kg x 15 mg/kg = 1230 mg or ~1200 mg/mo.

What would be appropriate for this patient?
This patient meets the criteria for using a CGRP antagonist because she has tried 2 preventive treatments for more than 60 to 90 days. Erenumab is not the best option, given the patient's history of hypertension and IBS-C. The patient fears hospitals and IV medications, making eptinezumab a less-than-ideal choice. Depending on her insurance, fremanezumab or galcanezumab would be good options at this time.

CGRP antagonists have not been studied or evaluated in pregnancy, but if this patient becomes pregnant, a first-line agent for prevention would be propranolol, and a second-line agent would be a tricyclic antidepressant, memantine, or verapamil. Avoid ergotamines and antiepileptics (topiramate or valproate) in pregnancy.[43,44]

The challenges associated with MAbs

MAbs can be expensive (**TABLE 2**),[45] some prohibitively so. On a population scale, biologics account for around 40% of prescription drug spending and may cost 22 times more than small-molecule drugs.[46] Estimates in 2016 showed that MAbs comprise $90.2 billion (43%) of the biologic market.[46]

MAbs also require prior authorization forms to be submitted. Prior authorization criteria vary by state and by insurance plan. In my (ES) experience, submitting letters of medical necessity justifying the need for therapy or expertise in the disease states for which the MAb is being prescribed help your patient get the medication they need.

Expect to see additional MAbs approved in the future. If the costs come down, adoption of these agents into practice will likely increase. JFP

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