



The next generation biopharma leader



Biologics Trend Report

Sponsored by UCB, volume 1



Dear Health Care Professional

The pharmaceutical industry is engaged in an exciting era of progress. Scientific research, backed by growing knowledge of the human genome, is realizing the promise of personalized medicine. As we gain a greater understanding of the human body's biological processes, we have been able to develop therapies that impact these processes, bringing a different approach to the treatment of disease.

Biologic drugs have brought treatments to many conditions for which patients have had few options until now. Often these drugs are targeted therapies that allow physicians to home in on the mechanisms of action for many conditions. As an unprecedented number of biologic drugs move through the development pipeline and reach the marketplace, more and more patients are becoming the beneficiaries.

However, this scientific achievement is not inexpensive. Some biologic drugs can cost tens and even hundreds of thousands of dollars per patient per year. Ensuring that the right patient is prescribed the right drug at the right time — and at the right price — is now more critical than ever.

Since the costs of biologic drugs continue to be a major driver of health care spending, insurers are taking a more active approach to managing these therapies and the conditions they treat. Gastroenterology and rheumatology specialists employ a large range of therapies in treating large patient populations and multiple conditions. Many of these treatments are biologic drugs.

The first edition of the *Biologics Trend Report Sponsored by UCB*, Volume I, is based on information gathered from surveys of managed care professionals, PBM and specialty pharmacy executives, gastroenterologists, rheumatologists, and office reimbursement specialists. It addresses many of the issues that concern these constituencies today, including:

- Management trends for biologics that impact managed care organizations most often, and the trends that are likely to emerge in the next few years
- The conditions that health plans rank as their highest concerns
- Issues that physicians are experiencing in the reimbursement of biologic therapies
- Operational improvements that providers are implementing to make their businesses more efficient
- The role of PBMs and specialty pharmacies in managing conditions in rheumatology and gastroenterology
- The ways in which health plans, PBMs and specialty pharmacies, and physicians work with manufacturers on pricing and rebates for biologics that treat gastroenterologic and rheumatologic conditions

We would like to extend our thanks to all the survey respondents for their participation. We hope that you find the *Biologics Trend Report* useful in understanding biologics and their impact on the gastroenterology and rheumatology markets.

Sincerely,

W. C. (Bill) Williams III, MD
Executive Vice President
National Association of Managed Care Physicians

John A. Hardin, MD
Chief Scientific Officer
Arthritis Foundation

Sponsors and Report Advisory Board

Sponsors



UCB Inc.
1950 Lake Park Drive
USA Smyrna, GA 30080
+1 770 970 7500
www.UCB-Group.com



National Association of Managed Care Physicians
4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
www.namcp.org



Arthritis Foundation
P.O. Box 7669
Atlanta, GA 30357
800-283-7800
www.arthritis.org

Executive Editor

Peter Sonnenreich
Kikaku America International
2600 Virginia Avenue, N.W. Suite 517
Washington, DC 20037
202-338-8256
Fax 202-337-3496
info@pharmaamerica.com

Advisory Board

Report Chairmen

John A. Hardin, MD
Chief Scientific Officer
Arthritis Foundation
Atlanta, GA

W. C. (Bill) Williams III, MD
Executive Vice President
National Association of Managed Care Physicians

Managed Care Medical Director and Pharmacist Advisors

Marc Dinnel, RPh, MBA
Director of Pharmacy
MercyCare Insurance Company
Janesville, WI

Terrance A. Killilea, PharmD
President
Medical Cost Solutions LLC
Eagle, ID

Bonnie J. May, RPh, MBA
Injectable Clinical Pharmacist
Fallon Community Health Plan
Worcester, MA

Dan Ollendorf, MPH
Executive Director
Health Economics and Outcomes Research
Launch & Brand Business Line
IMS Health
Watertown, MA

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Baltimore, MD

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CEO and Managing Partner
BioPharma Partners
OncoMed; YgeneX
Manhasset, NY

PBM and Specialty Pharmacy Advisors

Jason Boeshans
Pharmacy Manager
PharmaCare Specialty Pharmacy
Portland, OR

Kevin Cast
Vice President, Pharma Sales
CuraScript Pharmacy
Orlando, FL

Stephen B. Cichy
Vice President, Business Development and Commercial
Operations
Option Care, Inc
Deerfield, IL

Jeff Martin, PharmD
Clinical Account Director
Innoviant
Hudsonville, MI

Rebecca Shanahan
President
Shanahan Capital Ventures LLC
Winter Park, FL

Debra A. Thompson, RPh
Branch Manager, Dallas Branch
CVS-Caremark Specialty Pharmacy
Richardson, TX

Gastroenterology Advisors

Crohn's & Colitis Foundation of America
New York, NY

David A. Johnson, MD, FACC, FACP
Professor of Medicine
Chief of Gastroenterology
Eastern Virginia Medical School
Norfolk, VA

Seymour Katz, MD
Nassau Gastroenterology Associates, PC
Great Neck, NY

Beth-Ann Norton, MS, RN, CS
Adult GI Nurse Practitioner
MGH Crohn's and Colitis Center
Massachusetts General Hospital
Boston, MA

Bruce E. Sands, MD
Assistant Professor of Medicine
Harvard Medical School
MGH Digestive Health Center
Massachusetts General Hospital
Boston, MA

Rheumatology Advisors

N. Nichole Barry, MD
Sports, Orthopedic, and Rehab (SOAR)
Redwood City, CA

Mark Genovese, MD
Associate Professor of Medicine
Co-Chief, Division of Immunology and Rheumatology
Stanford University School of Medicine
Palo Alto, CA

Robert A Harrell, MD
Durham Rheumatology
Durham, NC

Robert Herman, MD
Goldstein, Siegel, Herman, Goldman, MD, PC
Great Neck, NY

Dina Titova, MD, PhD
The ROAD Clinic
Lakewood, WA

Jack Waxman, MD
Northern California Medical Associates
Santa Rosa, CA

Physician Office Advisors

Lorraine Schmidt
Office Manager
Arizona Gastroenterology and Therapeutic Endoscopy
Scottsdale, AZ

Fred May, MD
Madison, MS

Contributing Writers

John Carroll
Wallingford, VT

Mary Anne Dunkin
Roswell, GA

Mari Edlin
Sonoma, CA

Steve Frandzel
Atlanta, GA

Contributing Editor

Toni Rosenberg
Newton, MA

Marketing Research and Analysis

Brian Gallick
Co-founder, Vice President of Product Development
CareCircle
Pleasantville, NY

Andy George
Monroe, CT

Dudley "Skip" Gill
President
Strategic Impact Marketing
Lakewood, CA

John Mack
President
VirSci Corporation
Newtown, PA

Graphic Design

Robert Bell
K+A Creative
Frederick, MD

Joshua Phillips
The CementWorks
New York, NY

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Executive Summary

The complexity of gastroenterology and rheumatology, combined with the evolution of public and private reimbursement and payment policies, has generated a range of perspectives on the management of biologic services and the costs of care. The *Biologics Trend Report Sponsored by UCB*, Volume I, gathers the experience and opinions of health plan organizations, PBM and specialty pharmacy leaders, gastroenterologists, rheumatologists, and gastroenterology and rheumatology administrators, and considers the implications for policy and change among these key constituencies.

What follows are primary findings from each of the five surveys.

Managed Care Community

Surveys were sent to 1,500 managed care medical directors and pharmacists. Research was fielded from April 22, 2008, to June 3, 2008. The survey was designed to assess current practices in health plan management of biologic drugs in the areas of gastroenterology and rheumatology. Ninety-eight managed care professionals responded to the survey. Questions focused on the following:

- Management tools for controlling the cost of biologics
- Criteria for approvals and denials of biologics
- The value proposition of biologics
- Patient-support programs for biologics

Primary Managed Care Findings

The rapidly rising expense of supplying biologics to members is spurring pharmaceutical experts at U.S. health plans to look over a broad array of new management tools to make sure that the right therapy is going to the right member at the right price.

Managed care organizations are gaining more experience with biologics. In the next year or two, as they try to acquire any advantage possible in leveraging lower

prices for the biologics they deem most important for their membership, many health plans will press for more involvement by specialty pharmacy providers.

At a time when the use of generic drugs continues its ascent, it is also clear that once biosimilars become available, managed care organizations will move quickly to give them a preferred status in the drug plans they offer.

PBMs and Specialty Pharmacies

Surveys were sent to 1,200 PBM, mail service, and specialty pharmacy professionals. Research was fielded from April 22, 2008, to June 6, 2008. The survey was designed to assess specialty pharmacy strategies and services for biologic drugs in the areas of gastroenterology and rheumatology. Fifty-eight PBM, mail service, and specialty pharmacy professionals responded to the survey. Questions focused on the following:

- Services offered by specialty pharmacies to patients, plans, and manufacturers
- Utilization management tools and cost-containment strategies
- Distribution methods for fulfilling patient medication orders
- Conditions that health plans are most concerned with managing

Primary PBM and Specialty Pharmacy Findings

Most PBMs and specialty pharmacies expect the prices of injectables and infusibles, both physician- and self-administered, to continue to increase over the next year.

PBMs and specialty pharmacies offer payers a wide range of patient services — such as processing prior authorizations — to support prescription management.

Most PBMs and specialty pharmacies apply utilization management tactics, either voluntarily or because the strategies are mandated by health plans; prior authorization was cited as the number one strategy.

PBMs and specialty pharmacies distribute biologics through overnight and mail-order delivery, along with other means, in order to deliver these treatments to patients in a timely manner.

Gastroenterologists

Survey letters were mailed to 6,700 gastroenterologists. Research was fielded from May 16, 2008, to June 16, 2008. The survey was designed to assess current perspectives in regard to the use of biologic agents to treat patients with CD. One hundred and twenty-one gastroenterologists responded to the survey. Questions focused on the following:

- Frequency of prescribing biologics for patients with CD during the past year, along with expectations for future prescribing
- Factors considered when prescribing biologics for patients with CD
- Reasons for stopping biologics or switching to another agent
- Experiences with obtaining prior authorizations and approvals for biologics

Primary Gastroenterologist Findings

Gastroenterologists are very interested in biologic agents for their Crohn's patients, and are prescribing them more frequently; they believe that by reducing symptoms, these drugs improve their patients' quality of life.

Many gastroenterologists expect to increase the number of prescriptions they write for biologics when other treatment options fail, or even as first-line therapies.

Most of the surveyed clinicians indicated their belief that the biologic agents currently in use greatly diminish the need for hospitalizations, and that these agents are no more costly than hospitalization or the procedures that are required for treating patients with CD.

Many clinicians believe that insurers' stringent preauthorization and appeals processes for biologics unnecessarily

extend the time a Crohn's patient waits before receiving a much-needed therapy, and that this compromise to the best possible care may become even more prominent as use of biologic agents continues to expand.

Rheumatologists

Survey letters were mailed to 3,400 rheumatology practices. Research was fielded from May 16, 2008, to June 16, 2008. The survey was designed to assess current practices in the prescription of biologic agents for rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis. Ninety-eight rheumatologists responded to the survey. Questions focused on the following:

- Use and effectiveness of biologics in rheumatology practice
- Rheumatologists' prescribing patterns for biologics
- Challenges that rheumatology practices face in obtaining insurance coverage for biologics
- Rheumatologists' opinions on biologic agents in the pipeline

Primary Rheumatologist Findings

All of the physicians who responded to the survey prescribe biologic agents to selected patients.

Most respondents agree that the biggest drawback to these new agents is cost; without insurance coverage, few patients can afford biologics, but for many, even insurance co-pays are prohibitively expensive.

Often reluctant to cover biologics on account of their cost, insurers typically require excessive preauthorization procedures that deplete the time of physicians and their staff members. More than half of the respondents indicated that they have had to hire additional staff — or are planning to hire — in order to handle access-to-care problems.

Despite the obstacles, physicians said they will continue to prescribe biologics. Eighty percent said they anticipate increasing the number of prescriptions they write for biologics next year.

Coding and Reimbursement

Survey letters were mailed to 10,100 gastroenterology and rheumatology practices. Research was fielded from May 16, 2008, to June 19, 2008. Physicians were asked to fill out the gastroenterologist or rheumatologist survey and to give the reimbursement survey to their office reimbursement specialist. The survey was designed to assess current practices and challenges in billing and coding in rheumatology and gastroenterology offices. Sixty-three gastroenterology and rheumatology reimbursement professionals responded to the survey. Questions focused on the following:

- Trends in billing and reimbursement
- Payment trends among health insurers
- Plan profitability and contract negotiation
- Diagnostic procedures and biologics most often associated with reimbursement problems

Primary Coding and Reimbursement Findings

The average wait for a new-patient appointment exceeds 20 days. Shortening the wait so that it is 48 to 72 hours would increase the number of these visits, which are typically more profitable, and would avoid alienating prospective patients and their referring physicians.

Almost one-third of respondents reported that most of their managed care plan contracts are not profitable, and 16% said they do not know whether these contracts are profitable or not. An analysis of these relationships would be essential to any practice that wants to remain profitable.

Many respondents said that plans are inconsistent in their allowables, fees, acceptance of first claims, and speed of payment.

Many respondents are unaware of the appeals options that most plans offer. Understanding these options and the procedures for pursuing them would assist practices in resolving problems with claims that are incorrectly paid.

Managed Care Community



In recent years, the rate of spend of the pharma benefit at U.S. health plans has been tempered by a steady rise in the number of less expensive generic prescriptions. But the use of biologics — and the costs associated with them — are rising fast.

One reason for rapid growth in the use of biologics, according to the managed care professionals who responded to the survey and a group of pharmacy experts who were queried on the results, is their clear impact on the lives of patients. In refractive and severe cases, the new generation of biologics can make a significant difference in patients' quality of life day-to-day.

But the high cost of these drugs is leading managed care pharmaceutical professionals to evaluate a host of new measures to help control the use of biologics — when appropriate. Health plan professionals are moving methodically, taking care not to add to their plans' costs when someone else bears the risk of the expense. And while prior authorization for drug use has become a standard approach with a large majority of plans, pharmacy executives are also assessing a long line-up of new strategies that can offer an added measure of control.

As they gain more experience with biologics, plan executives are crafting a more straightforward approval process for physicians, with the intent of shortening the turnaround on coverage decisions.

Health plans are seeking more favorable prices that can be leveraged through a wider selection of biologics. Many health plans say that once biosimilars are available in larger numbers, they will become a required first step, just as plans often require that a traditional therapy be tried before use of a biologic can be authorized.

Biologics are now a standard component of the drug benefit offered by U.S. health plans. But the strategies used to manage them are still evolving.

Ninety-eight health plan pharmacists and medical directors responded to the survey. Pharmacy directors made up the largest group (42%), followed by clinical pharmacists (22%), medical directors (18%), and senior managers (9%). This composition helps explain why 81% of the respondents hold either a PharmBS or a PharmD. Twenty-two percent of the respondents are MDs.

Sixty percent of the respondents work for a health plan, with 16% in an integrated delivery system. About half (48%) of the organizations represented in the survey are situated in a local area or a single state. Twenty-eight percent of the surveyed organizations are regional in scope, and 22% are national. The size of the organizations surveyed varies widely, from the 30% that cover fewer than 100,000 lives to the 17% that cover more than 2.5 million lives. Most of the surveyed plans are HMOs or PPOs.

“Costs for infused and self-injectables, on average, are rising faster than costs for other therapies, according to managed care respondents.”

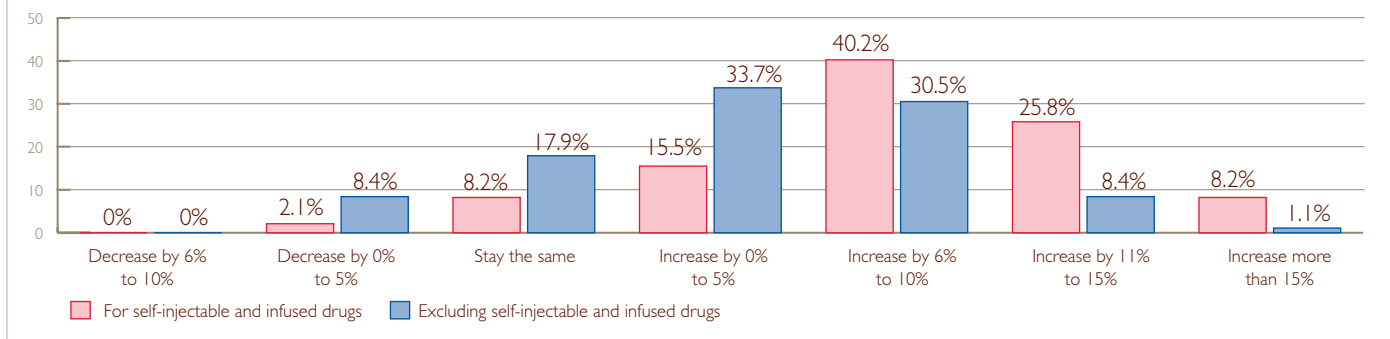
Costs for infused and self-injectables, on average, are rising faster than costs for other therapies, according to respondents (Figure 1). About one in four respondents said prices for these biologics are likely to grow 11% to 15% over the next 12 months, and 40% predicted price hikes of 6% to 10%. The survey analysts weren't at all surprised.

“Excluding infused and self-injectables, it's pretty flat,” said John Fox, MD, medical director at Priority Health in Grand Rapids, Michigan. “Many are seeing plus or minus 5%. I would conclude that the majority of people see costs increasing

more than 5%. The primary driver is still going to be non-self-injectables. Right now most costs for infusibles are covered under the medical benefit, where the routine cost trend is 10% to 12%, driven by the oncologics.”

“It looks like the same thing we're experiencing,” said Fred May, MD, medical director at Blue Cross & Blue Shield of Mississippi in Flowood. “Injectables are driving cost. And we've gone pretty hard-line against the new drugs that have come out. They're more about convenience, extended release, and so on.”

Figure 1: What is your expectation of pharmacy cost trends in the next 12 months?



Marc Dinnel is pharmacy program director for MercyCare Health Plan in Janesville, Wisconsin. “There are two drivers,” he said. “One is the darn cost of the drug, and the other is utilization. For us it seems like infusibles — especially in oncology — are experiencing higher and higher utilization.”

“Over the last 12 to 18 months, we’ve also seen an increase in utilization of the self-injectables,” Dinnel continued. “The rheumatologists seem to go to the biologic self-injectable much faster than they did in the past. Instead of milking patients along with methotrexate for a year or so, they’re moving to the next therapy much faster.”

Dermatologists and gastroenterologists are also moving patients to the next therapy more quickly than they used to.

“It seems easier to get access to infused [drugs] than [to] injectables,” added Dinnel. “Pharmacy benefits are so much easier to control, while medical benefits are much harder to manage. We put in prior authorization and sent out many letters explaining that J-codes are required for prior authorization. We push to self-injectables first rather than infusibles.”

One expert sounded a note of caution on the overall cost trend.

“Increases from year to year have not been something you could easily graph,” said Bonnie May, RPh, a clinical pharmacist for Fallon Community Health Plan in Worcester, Massachusetts. “It’s an up-and-down thing, and there’s no consistent upward or downward trend. Six percent to 10% would be my own educated guess on what will happen in the next year, but the numbers have been all over the place.”

Most respondents noted a rise in the co-pay amounts that members are responsible for in tiers 1 to 5 within the drug formulary. The biggest difference was between

tiers 2 and 3, where the co-pay jumped from a response average of \$20 to \$35. Fewer respondents had co-pays for a fourth and fifth tier.

None of the individual experts interviewed had five tiers, and a preference was evident for limiting tiers to no more than four.

“I think another way of looking at this is generic, preferred, non-preferred, and a specialty tier,” said Fox. A general trend emerges toward significant differentials in the amount that members are paying when they move from one category to another. “Five or 10 dollars between tiers usually isn’t enough to persuade patients. You need 20 or more dollars between tiers to drive patients. I’d expect to see the differential widen.”

“We have four co-pays in all,” said Fred May. “We can put anything we want anywhere, a generic on the fourth tier, and so on. Most goes by pricing, if not more on efficacy, because even if a drug is efficacious, we don’t want everybody on it. If generics work perfectly well, why direct patients to other therapies? You could do step therapy but it’s a nightmare. You need patient histories.” With many members coming in from other plans or facing unknown complications, “It’s not as easy as it sounds,” he added.

“I don’t think there are a lot of folks that have tier 4 and tier 5,” observed Bonnie May. “They are either carve-outs, or they just threw everything into tier 3. If it’s a drug benefit, it’s three tiers. For a medical drug benefit, we don’t have tiers. The member pays nothing.”

“For the most part it’s pretty stable,” said Dinnel. “As groups renew, more and more are choosing a three-tier plan. Our average co-pays would stay the same. We have some plans that are just one and two tiers, and there’s a migration to a third, but the co-pays aren’t going up. I think they’ll stay stable for a couple of years. A \$75-to-\$100 co-pay is kind of unsettling. People just think you have bad

insurance. We are increasing premiums rather than the co-pay.”

Survey respondents could assign a percentage for co-insurance for up to five tiers, and the number rose from 6% in tier 1 to a 16% average in tier 3 before dwindling again.

“We don’t do co-insurance for ours, though some do it,” said Fred May. “Co-insurance is still popular for the highest tier. We did it one year and didn’t like it. On the fourth tier, we wanted cheaper drugs we didn’t want people to use.”

“This [patient percentage for co-insurance] is much lower than I expected,” offered Bonnie May. “I’ve been hearing as much as 25% in tier 3. That seems a common number.”

“We have a migration to more co-insurance,” said Dinnel, but he added that the trend is stable, and “the percentages have not changed.”

Managed care pharmacy experts generally defined biologics broadly (Figure 2). Just over half of the respondents consider a biologic any “extremely expensive” therapy. Two-thirds define a biologic as any drug that is produced with recombinant DNA technology.

“I don’t think there is an industry standard [for the definition of biologics],” said Bonnie May. “Part of the problem is that there are different answers and interpretations.” Her plan’s definition, she said, is a combination of medications produced through recombinant DNA technology, medications that are nearly identical to the body’s own key signaling proteins and monoclonal antibodies.

“All of these are definitions of biologic drugs,” noted Dinnel. “From a benefit perspective, the last two in the survey list [recombinant DNA and extremely expensive drugs] are the most accurate.”

Several respondents suggested there is no need to come up with a single definition for biologic or non-biologic drugs in order to manage the benefit — though they suggested that a clear definition could help others in their business better understand pharmacy trends.

“From a tier perspective, it’s irrelevant how we define biologics, unless there’s a separate benefit design,” said Fox, whose plan gathers all expensive therapeutics in a specialty therapeutics category, whether they’re small molecule drugs used to treat cancer or antibodies.

“You don’t need to define it to manage it,” added Bonnie May. “We manage it by price. A definition is for people who are not in the pharmacy department so they can follow what’s going on.”

Figure 2: How does your organization define biologic drugs?

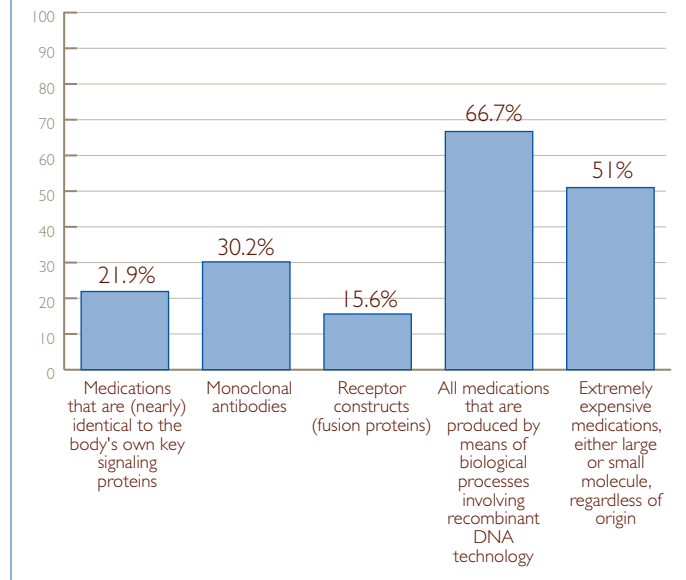


Figure 3 indicates respondents’ belief that the best candidates for biologic therapy are those who have failed a non-biologic drug (84%) or patients with severe or refractive disease (65%). Respondents were much less likely to green-light biologics for newly diagnosed patients (27%) or patients with mild-to-moderate inflammatory disease (26%).

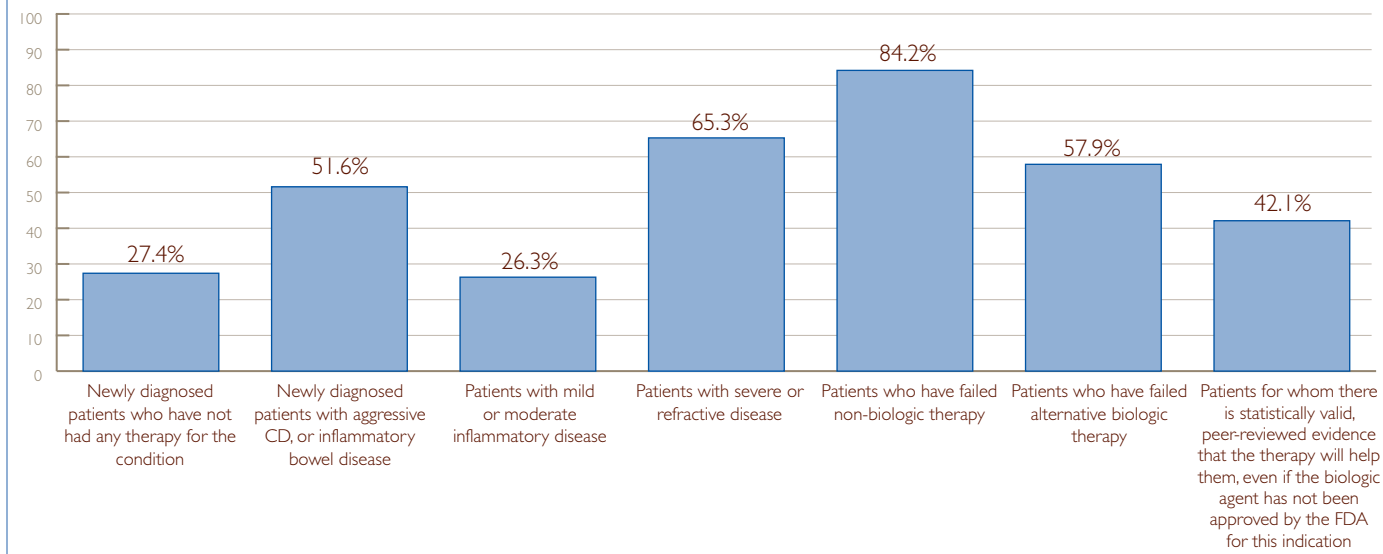
“We would generally be reluctant to give biologic agents to folks with mild-to-moderate or newly diagnosed cases that are therapy naïve,” said Bonnie May. “A lot of this has to do with the cost. We’re reluctant to have them jump right in with the most expensive medications. A lot of these drugs are so new, there’s no long-term proven efficacy and safety. And I have heard other pharmacists say that if you start with the big guns and they don’t work, you don’t know where to go next.”

“Most of the time you’re going to have a failure of traditional therapies first,” agreed Dinnel. But for patients with newly diagnosed multiple sclerosis (MS), “most likely you’ll put them on a biologic. Some conditions warrant the use of biologics.”

“For newly diagnosed patients with aggressive diseases who then fail other therapies — methotrexate for Crohn’s and rheumatoid arthritis — plans are aggressively managing cases,” said Fox. “We’re in the intensive management category, and the trend generally is to manage these categories more aggressively.”

But the cost is steep once a member makes the transition

Figure 3: Which of your plan's members are candidates to receive biologic therapy?



to a biologic. Every time someone goes on a biologic, Fox explained, a plan is looking at five-figure expenses for the therapy on top of reimbursements to a specialist.

Respondents showed a preference for shifting biologics from the medical benefit to the pharmacy benefit, where a plan can more easily control the use of the therapy as well as the cost involved (Figure 4).

"We've covered ours as pharmacy benefits all along," said Fred May. "We stopped buy-and-bill right away and got a lot of flak from rheumatologists. They all wanted to inject. Centcor [the manufacturer of infliximab (Remicade®)] told rheumatologists right on its website they could make money off infusion centers. The problem with the medical benefit is you can't have prior authorization. Once they file a claim, the drug has already been given."

Dinnel also noted that more plans are covering self-injectables in particular on the pharmacy side. But not everyone sees a shift from medical to pharmacy as positive.

"A lot has to do with risk," said Bonnie May. "It may not be advantageous for us to offer something as a pharmacy benefit." If, for example, May went on to explain, the provider or provider group had a higher risk in the medical benefit than pharmacy, the preference would be to reimburse that drug under the medical benefit. "We're not paying for it; they are," she said.

"I see people moving in both directions," said Fox. "Some are moving to the medical benefit to reduce the cost of the pharmacy benefit, which is sold as a separate rider. Others are moving drugs from the doctor's office — [which fall under] the medical benefit — to a pharmacy benefit."

Most say that dose escalation is a serious issue (Figure 5). Slightly more than three out of four respondents in the survey ranked the level of seriousness at 4 or 5 on a scale of 5.

"It's a difficult problem to manage," said Fox, who added that the same basic issue comes up with nearly every drug, whether it's a biologic agent or not. "For patients with an initial response and a relapse, or those who don't have a good clinical response, the natural tendency is to think they need more of the drug, without any evidence to support this belief."

“Pharmacy executives are assessing a line-up of new strategies that may offer increased control in managing the costs of biologics.”

Plans can limit drug use to FDA-approved doses and then ask for clinical justifications for dose increases, said Fox. They can also set out policies on prior authorization that would request clinical evidence to back up a doctor's decision to escalate dosage. But most health plans are not able to look closely at doses.

"If it doesn't work," said Fred May, "the first thing anybody does is up the dose. Remicade is one of the worst ones. Some MS drugs seem to stop working,

Figure 4: For the years 2006, 2007, and 2008 (est.), how has your largest commercial health plan covered self-injectable biologics?

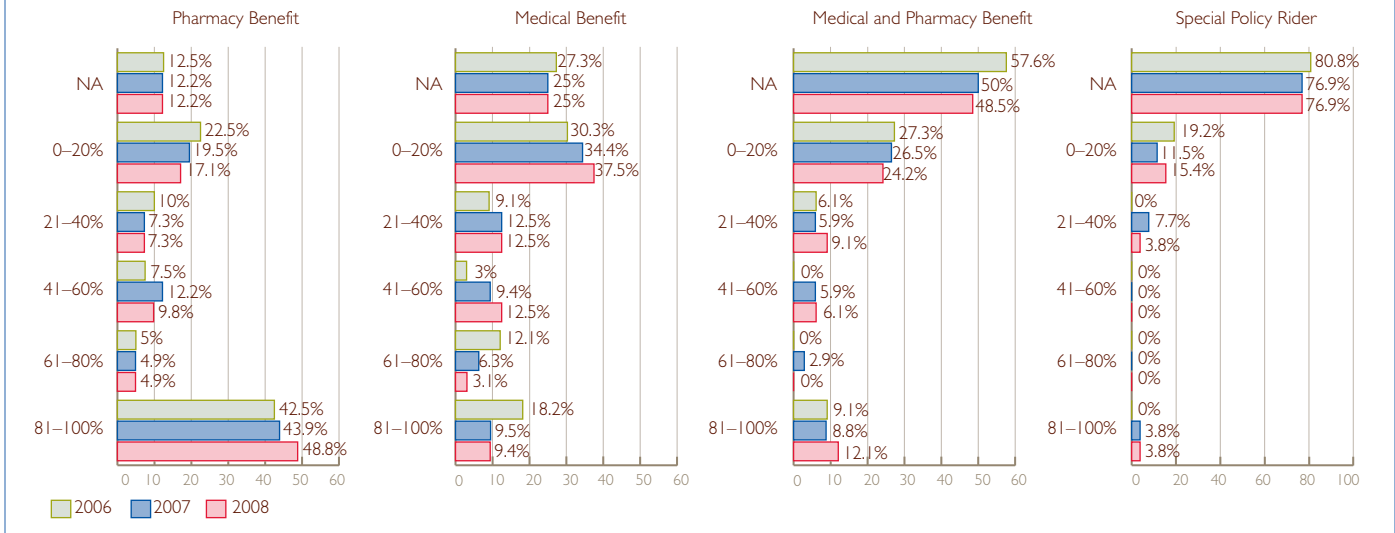
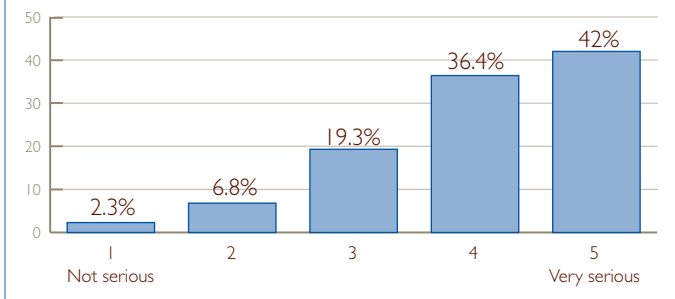


Figure 5: How serious a cost control issue is dose escalation of biologic agents?



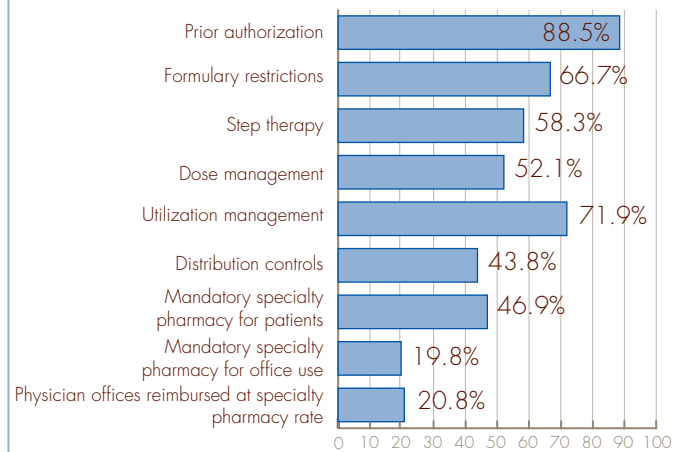
so they switch. We're somewhere in the middle of the scale — 3 to 4. It's something you just have to deal with."

"I think everyone is looking at utilization reports," said Bonnie May. "I'm even going down to the individual patient level to see over a period of time whether a dose is escalating — picking out individual doctors who are dosing folks on the high side or above what an average dose would be."

"I haven't gone to the doctors to find out what is going on," she added. "Is there more obesity, and are patients dosed by weight? If they have minimal response and a little is good, is more necessarily better? Often when people are using these biologic agents, they've failed everything else."

Fox was intrigued to see that a smaller majority of the surveyed plans use step therapy (58%) for biologics (Figure 6). "Step therapy simply says, I'll allow drug X if drug Y was used previously," he said. "Take methotrexate, for example. If you can buy methotrexate for a patient for \$500 a year, and Enbrel® is \$20,000, it's common sense to make sure methotrexate is used first. We want to make

Figure 6: What techniques do your health plans use to control the cost of biologics?



sure they took methotrexate, were compliant, and used it appropriately before moving from \$500 to \$20,000. Mandatory specialty pharmacy for patients [cited by 47% of respondents] is becoming increasingly common. It's a very significant trend."

"Reimbursement at a specialty pharmacy rate will predominate," Fox added, pointing to the technique cited by one in five respondents. But it won't be easy for providers. It's likely to present physicians — who may have five insurers demanding five specialty pharmacy arrangements — with a "logistical nightmare," he said.

Prior authorization appears to be close to an industry standard; 89% of respondents require it. "Everybody does it," said Fred May. "We're also starting to get mandatory specialty pharmacy for patients," he added.

"Either mandate specialty pharmacy use for drugs to be delivered to the doctor's office, or allow doctors to buy and bill but only reimburse at the rate for specialty pharmacy," said Bonnie May.

"I think these are all pretty common controls," said Dinnel, referring to the survey list of cost-control strategies. "When you check prior authorization, you are also checking formulary restrictions and utilization management. Those three items are intertwined."

"Distribution controls may increase," Dinnel added. "I think there's an opportunity to do some group purchasing or use specialty pharma a little more efficiently. Rather than moving away from having physicians buy and bill, if you can control it, then you have control over the cost."

The pharmacy department was cited most often (43%) as having the biggest influence over establishing prior authorization protocols (Figure 7), followed by the P&T committee (30%) and the medical department (21%). "That will be a mix anywhere," said Fred May. "We do pretty much pharmacy and medical, mostly medical. Our pharmacy director left a year and a half ago. We pretty much go by FDA rules."

There was also considerable consensus among survey respondents on the need for a quick response when a clinician asks to use a biologic (Figure 8). About 15% aim for a one-day turnaround, while 68% say they can provide an answer in one to three days.

"If you have adequate information," said Fox, "the turnaround should be quick." Some may take a few days to approve, Fox acknowledged, but he said he could not understand why anyone would respond in 20 days. "They may not understand the question," he suggested.

"In our case the prescription is faxed to a specialty pharmacy," said Fred May. "If it matches our criteria, they get it. If there are holes, they ask questions about why it didn't meet the criteria, and they send it to us, and we call and ask why. Most get it on the first day and the rest in one to three days."

"Ours is one to three days," said Bonnie May, "which is what Medicare requires. An answer must be rendered in so many hours. It's easier to do everything across the board the same way."

Some outliers in the survey appear to be pushing a minority of the respondents past 10 days, noted Dinnel, who added that very few managed care organizations will take anywhere near that long to respond.

Figure 7: What is the contribution of each of the following to the development of your organization's prior authorization protocols?

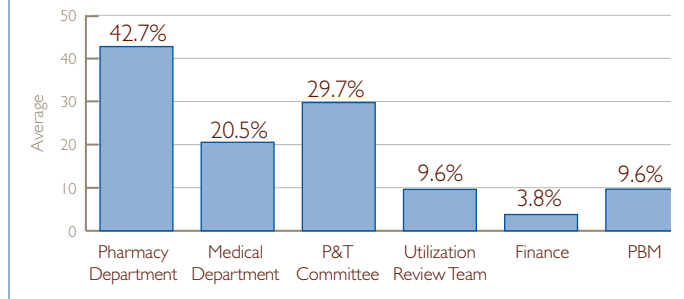
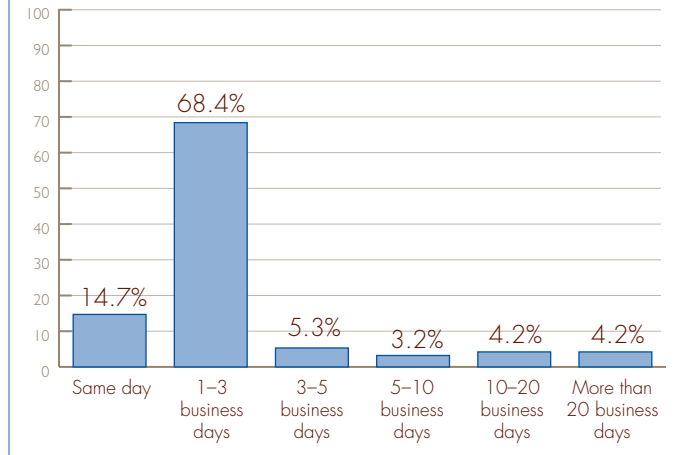


Figure 8: On average, how long does your organization take to inform the clinician of its initial decision to approve or deny use of a biologic agent?



Respondents indicated that managed care plans' use of specific criteria for prior authorization of biologics led to an average initial denial rate of 22%. About one in four of those decisions is reversed on appeal. But the denial rate may soon drop.

"It's a good return on your investment if you can avoid paying 15 out of 100 requests," said Fox. But many of these rejections are likely due to ensuring that the appropriate therapy is being used, and a plan can enforce a preferred status versus non-preferred status. "Our denial rate for first use of Enbrel is only 8%. Our denial rate for first use of Remicade is higher: 14%."

"I'm not really shocked," said Bonnie May. "Our own experience is a denial rate of 15% to 18%, and maybe 5% of the decisions are reversed. There may be a couple of things. Pharmacists making requests are more familiar with the criteria. I guess we almost try to second guess whether it's likely to be appealed and what the appeals

Figure 9: Which of the following conditions are in your top five priorities for managing health care costs?

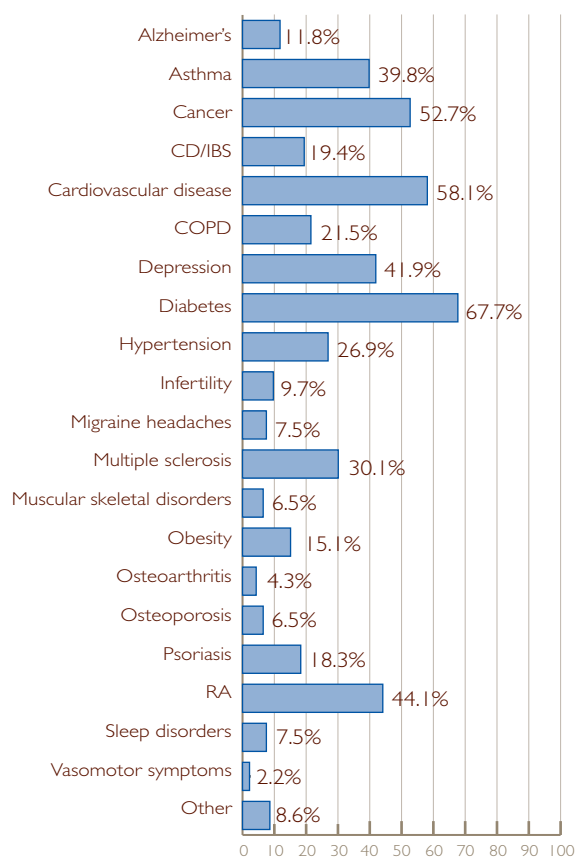
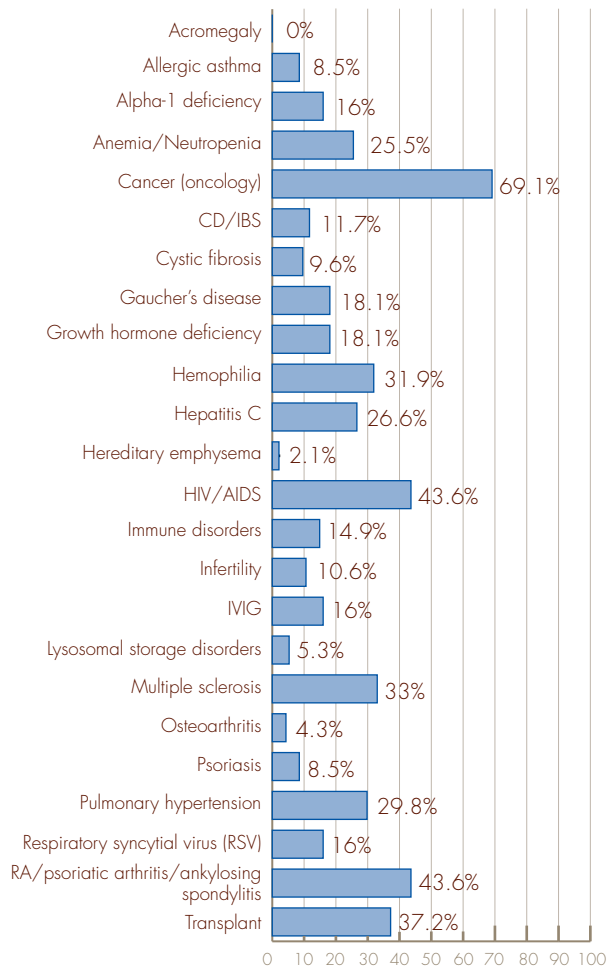


Figure 10: Which five of the following conditions are the most expensive to manage per member for your organization?



folks will do. But we're not quick to reject and are comfortable with the answer."

"We don't keep that number," said Fred May, referring to denial rates. "It's not terribly valuable. Most of the time the decision is overturned."

Dinnel agreed. "Specifically for biologics," he said, "[we] say we require traditional therapies first." But many times there's no indication that the patient has tried a traditional therapy, and a denial is issued. "We contact the physician. On appeal, the patient delivers information that he took this drug three years ago, when he or she was not on the plan." After receiving the new information, the plan approves the biologic.

The survey found that diabetes, cardiovascular disease, and cancer are the three top disease priorities for managing costs (Figure 9). They were followed by RA and asthma. But when the question shifted to costs broken down on a per-member basis, cancer, HIV/AIDS, and RA/psoriatic arthritis/ankylosing spondylitis rose to the top (Figure 10).

Various considerations have an impact in establishing priorities, noted Fred May. "You need to know what

are the most costly therapeutics, and what can you do something about," he said. "Plans should focus on what they can do something about," he added. "We go after cardiovascular, which costs us a lot of money. We go after the biologic area too. It's pretty easy. We make them go through a specialty pharmacy, where we get a pretty good discount, and we stay with the FDA decisions."

"Hypertension seems high," said Dinnel. "Combined with cardio, it ranks up there."

Fox, like some of his colleagues, said he was a little surprised by the survey responses in regard to individual costs that are associated with specific diseases. A disease like Gaucher's is rare, he said, but responses indicated that it is extraordinarily expensive to treat. Enzyme replacement therapies are also costly. Other so-called orphan diseases, for which treatment can go to six figures for a single patient, meet with the same challenges.

The status quo presents significant challenges when it comes to managing biologics.

The survey asked respondents to consider a variety of tools for managing the use of biologics. For the most part fewer than one in four respondents indicated current use of any one tool on the list; however, between 30% and much more than 50% said they are likely or very likely to try using the tools (Figure 11).

“Everything on the list is aimed at reducing costs by finding alternatives to existing practice,” said Fox.

Nine percent of respondents said they have a protocol for switching patients from branded to generic biologics — the generic product typically is rarely available — but 68% said it is likely or very likely that they will acquire such a protocol. Fifty-three percent said they are likely or very likely to adopt dose-management protocols, while 48% said they are likely or very likely to mandate a self-injectable over an infused product.

“When you take a drug that costs \$20,000 a year, I have another \$2,000 of infusion costs, [compared with] co-pays of \$500 on the pharmacy side of the benefit,” said Fox. “That’s the reason people are driving to self-injectables — it’s a better unit cost.”

“We started mandating specialty pharmacy 10 years ago, but everybody’s grasping now to do other things,” said Fred May. “You want to lower the cost without adding a lot of complexity, which adds a lot of expense administratively. With step therapy, the administrative costs can be tremendous.”

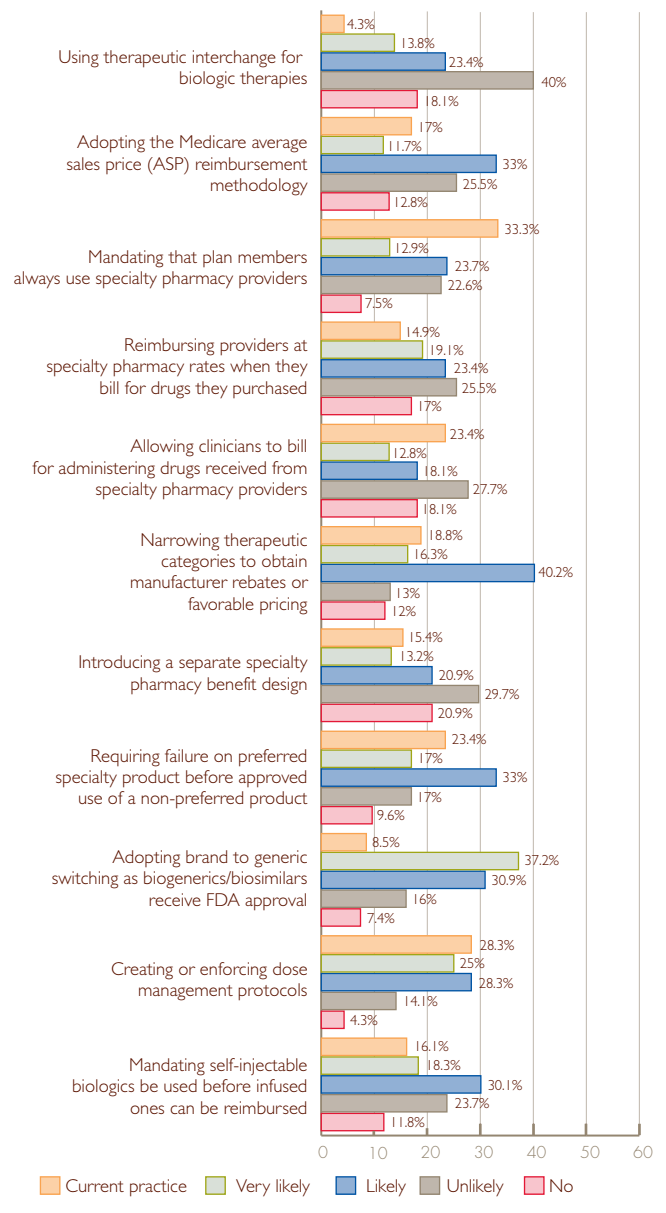
“I think we’re all struggling to identify the strategy that provides the best return,” said Bonnie May. “One survey result that surprised me is the finding that using therapeutic interchange is unlikely.” Only 4% cited therapeutic interchange as current practice. “I thought more folks would try to hop on board with that,” she said.

Thirty-seven percent ranked therapeutic interchange as a likely or very likely strategic move. And 56% say it is likely or very likely that they will narrow therapeutic categories to obtain better pricing.

“For rheumatoid arthritis, Crohn’s, and psoriasis, three or four drugs are available now versus one or two earlier,” Dinnel said. “With this choice comes an opportunity to choose preferred drugs. Manufacturers are starting to [offer] rebate[s] now that they’re starting to feel the competition.”

Most of the respondents either were not acquainted with patient support programs for specific biologics or said

Figure 11: Does your organization anticipate implementing any of the following in the next 12 to 18 months?

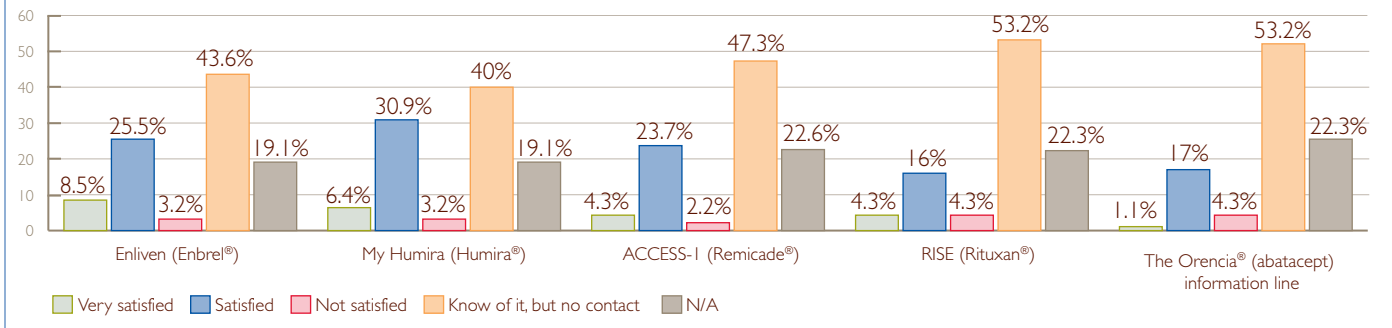


these programs do not apply to their plan (Figure 12). Respondents expressed deep skepticism in regard to the impact and goals of these initiatives.

“People aren’t using these programs,” said Dinnel. “It’s pharma’s attempt to develop further relationships with health plans, and health plans aren’t moving in that direction.”

“I don’t know how [managed care executives] know the program,” said Fox. “Health plans aren’t referring patients. Physicians are directing the manufacturer, and the manufacturer contacts the patient.”

Figure 12: How would you rate the following patient support programs?



“We don’t use these programs,” said Fred May. “We don’t endorse them. We try to stay away from pharma as much as we can.” He added that his plan does not object when physicians want to partner with manufacturers to educate patients. “But when you get into liaisons with pharmaceutical companies, it doesn’t work well. Nothing is turnkey. You have to have resources in your plan. Patients leave the program and come into the program. And the pharmacy business has been in flux, with acquisitions and changes. You never get a new rep with the same enthusiasm. And the company may lose enthusiasm and decide to go in another direction. We made a decision internally that the pharma support programs were not working for us. It’s hard enough with the programs inside your own walls.”

“We do most of our patient support and disease management in-house,” said Bonnie May.

The concept of broad patient support programs put in place by health plans, with a long list of potential strategies, warranted generally high marks by respondents (Figure 13). Such services as the availability of nurses to answer questions, compliance reminders, and phone consultations all ranked particularly high.

“Of course it’s going to decrease costs if patients learn how to inject themselves at home,” said Bonnie May.

“Health plans are looking at all sorts of ways to improve patient education,” noted Dinnel. “Case management programs, yes. For rheumatoid arthritis, we assume it’s being done by the office. We don’t have the resources to do it.”

Some strategies for improving patient awareness may lack sufficient data to prove real impact on a member’s health or on a health plan’s costs.

“Websites are nice,” said Fox, “but show me the evidence that they impact health.”

Almost half the respondents (46%) said they have no pay-for-performance plan in place (Figure 14). Among the 44% who said they have such a plan in place or are implementing one this year, most programs are aimed at primary care physicians.

“Pay-for-performance programs with primary care physicians can be significant — an additional \$25,000 on a base income of \$100,000,” said Fox. But for a specialist in cardiology who is earning \$500,000, that \$25,000 has a smaller effect.

“We have a pay-for-performance initiative for some of our providers, though not all of them,” noted Bonnie May. “One survey result I find intriguing is that even though about the same percentage of health plans have some sort of initiative, or plan to, than don’t, a lot of articles I’ve been reading refute the idea that this is a good way to practice medicine.”

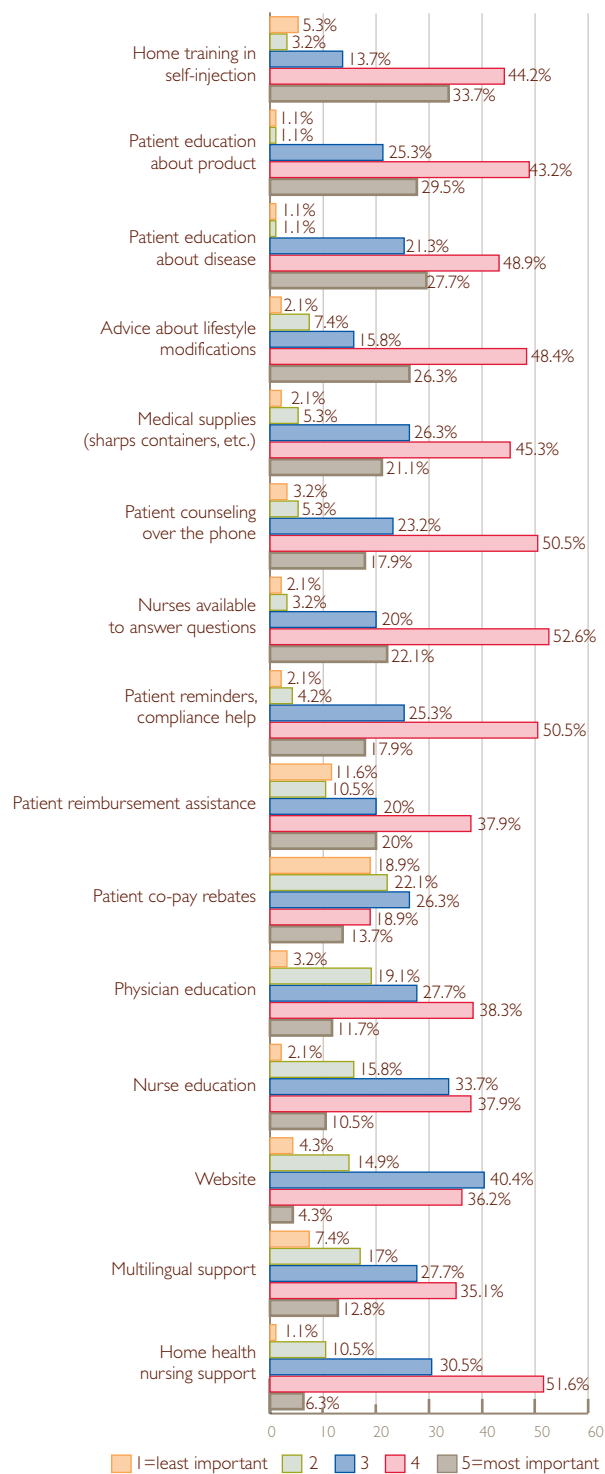
And these critiques are contributing to Bonnie May’s growing ambivalence.

Managed care respondents indicated a preference for shifting biologics from the medical benefit to the pharmacy benefit, where use and cost of therapies can be better controlled.

“Just because they get a bonus doesn’t mean they’re practicing good medicine,” she added. “I think eventually pay for performance will go away. They’ll come up with some other incentive program.”

“We don’t think pay for performance is effective,” asserted Fred May. “And we have a philosophical problem with it. We think [doctors] should all be top shelf.” It would make more sense to track their performance and punish them if they go astray from best practice guidelines, he added.

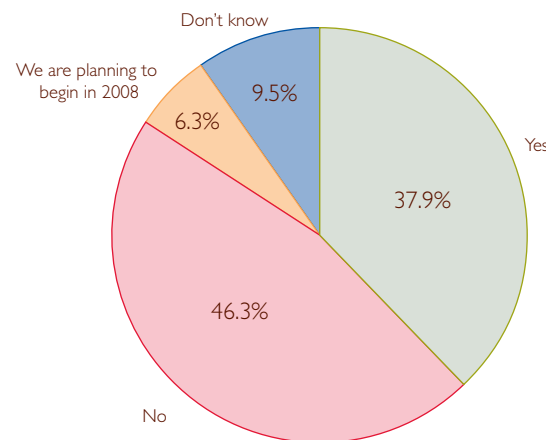
Figure 13: How important would it be for each of the following services to be offered in a patient support program?



"We don't want physicians to gerrymander patients and only pick ones who work with them. Diabetics are tough patients. Physicians shouldn't refuse to see tough patients."

If you do spend money on pay for performance, com-

Figure 14: Does your organization have any pay for performance (P4P) initiatives for providers?



mented Bonnie May, your biggest return is likely to come from primary care. "I hate to say that primary care physicians are the gatekeepers, but they see the patient first, and they have the best chance of keeping track of a patient's progress or lack of progress," she explained. "They're likely to refer a patient to a specialist and maybe coach the patient not to go to a specialist if they don't think it's necessary."

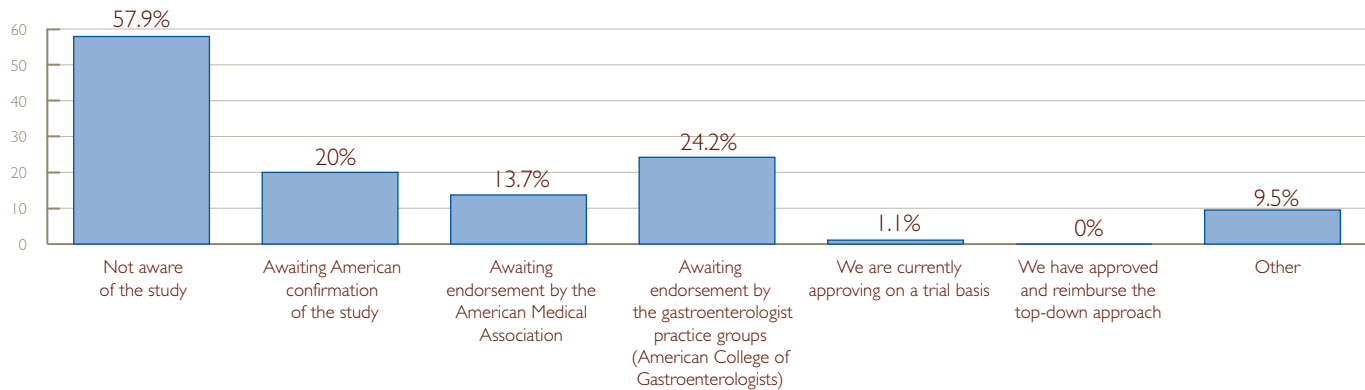
Most respondents were unaware of a recent European study that supports the effectiveness of a "top-down" therapeutic approach in treating aggressive CD (Figure 15). Among respondents who were aware of the research, most were waiting for an American confirmatory study or an endorsement from the relevant professional society.

"If you can get the same outcome with a less expensive drug, why use the top-down approach?" asked Fox. "If failure has no consequences, why use top-down? Why not start a patient on methotrexate and then switch to a biologic if the patient doesn't respond?"

For CD, patients can still respond to Remicade after failing methotrexate, and 38% of patients respond positively to methotrexate. "With cancer, you may want to use the top-down approach if you have one shot," said Fox.

"When biologics came out for rheumatoid arthritis, we went to the specialty societies and asked them whether they thought Enbrel or Remicade was better," said Fred May. "They were absolutely no help. It would be great if this were all laid out and they had a clear idea of where to go. I am a physician. I need more help than that, and they don't want to provide it. Most of the physicians who treat MS still don't know which drug is better. They're all different. Physicians can't make the decision because they can't figure out which treatment is better," he added.

Figure 15: Recently European researchers published a study regarding “top-down” therapy, in which biologic agents are said to be an effective course of treatment for patients with aggressive CD. What do you think of the top-down approach?



“There’s a tendency to want to start off patients with what appears to be the most powerful approach, but if it fails, where do you go?” asked Bonnie May.

Dinnel will wait for the specialist society’s endorsement of the top-down approach, but he doesn’t expect it anytime soon. “The specialty-physician organizations produce the guidelines for care,” he said, “and it takes them years. A study will be published, but it could take three to five years to establish that top-down therapy is the best course of practice.”

Large majorities of respondents either disagreed or remained neutral in regard to whether biologics can reduce costs or are no more expensive than hospitalization and the use of alternative therapies (Figure 16). Large majorities of the pharma executives also said they believe that biologics improve quality of life for their members and are appropriate for severe illnesses.

But it’s not always that straightforward.

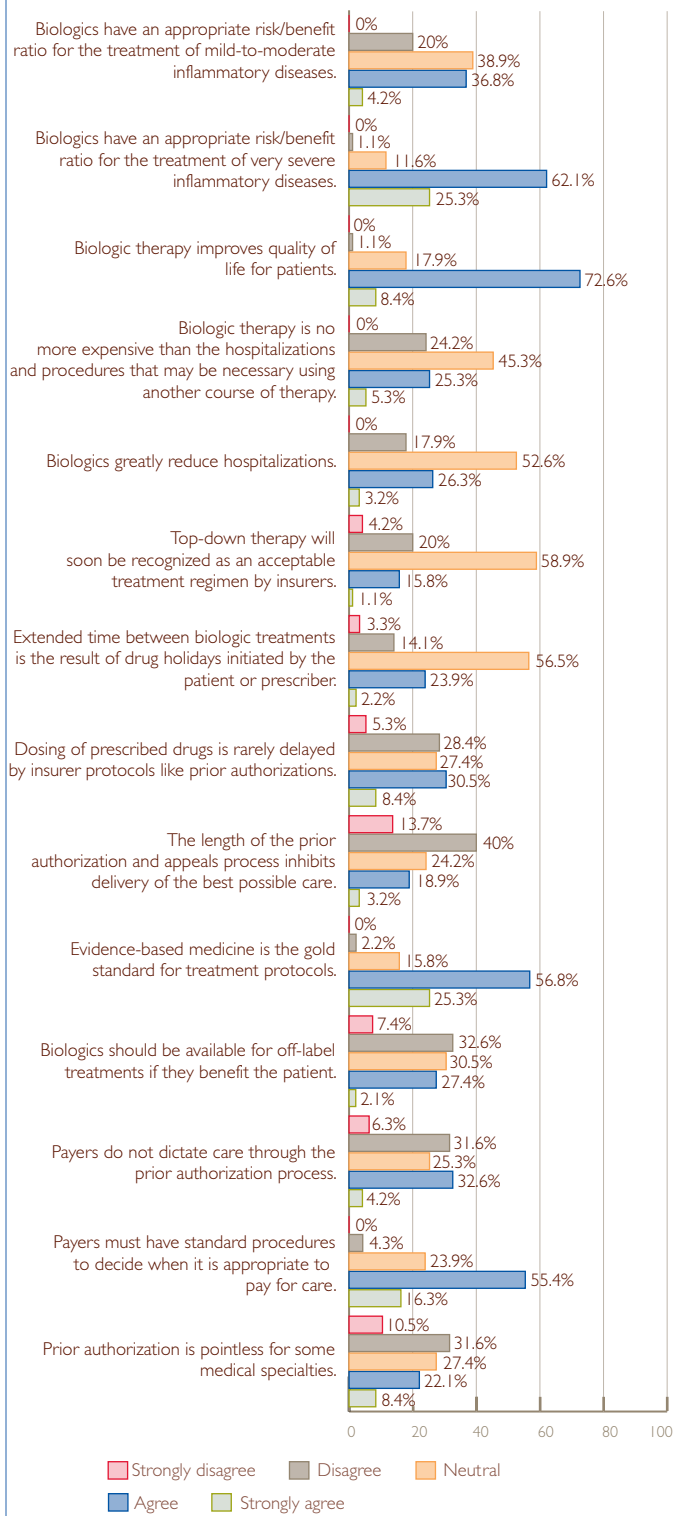
“We live in a very litigious state,” said Mississippi-based Fred May. “If we allow off-label use, we are saying that it is appropriate. If a patient has a problem, we could be liable because we sanctioned the use.” In addition, he noted, whether such treatments work for moderate disease is unclear. “For severe disease, we see a difference, at least initially. Almost anybody who gets Remicade will improve initially; then there’s dose creep and other issues, and eventually the improvement flattens out. But quality of life is improved for a short time.”

“It’s not always easy to get a reading on the cost of hospitalizations and other medical treatments that are not drugs,” said Bonnie May. “The information is not easily available. We all assume these drugs will reduce utilization, but this is an unproven assumption.”

Yet there’s no questioning the benefit that many biologics can provide to patients, Bonnie May maintained. “Rheumatoid arthritis is the most glaring example,” she said. “You see someone one day and she can’t perform the routines of daily living as she once could, like washing dishes. And then you see her after three months on one of the biologics and she feels great. She has a better attitude, and she can do more.”

“You see someone one day and she can’t perform the routines of daily living . . . And then you see her after three months on one of the biologics and she feels great . . . She can do more.”
—Bonnie May, RPh, clinical pharmacist for Fallon Community Health Plan

Figure 16: Please share your opinion on the following statements.



PBMs and Specialty Pharmacies



Biologic therapies are created from living cells. They are costly and require special handling, which frequently includes refrigeration. Typically they are administered by infusion or injection, often in a physician's office, but self-injectables and oral formulations have permitted patients to assume more responsibility for their own treatment.

The opportunity to cut down on the time and expense of visits to the physician's office affords patients an appreciable convenience. But with this convenience comes the possibility that compliance may suffer. Administration of biologics poses complications from the physician's standpoint as well: a rift has formed between many providers and payers as insurers have clamped down on reimbursement of these high-cost therapies. Further, manufacturers are finding themselves under closer scrutiny owing to hikes in pricing for biologics.

Specialty pharmacies and pharmacy benefit managers (PBMs) have a unique role to play in synthesizing the needs of all these stakeholders. They can help educate patients on compliance and on medication storage, administration, and side effects. They can distribute drugs both to patients and to physicians. They can help physicians with claims and can let them know if patients miss refills or encounter other problems with their medication. They can help plans by using prior authorization (PA), step therapy, and other tools to ensure that the right patient is getting the right drug at the right time. And they can work with manufacturers to help obtain drug rebates, favorable pricing, and co-pay assistance for patients.

PBM and specialty pharmacy participants responded online to the survey questions between late April and early June 2008. Nearly 85% of the respondents were practicing pharmacists; other respondents included pharmacy directors, medical directors, and senior managers, such as vice presidents. Respondents had been working in the specialty pharmacy field for an average of nearly eight years.

More than half of the respondents — 55% — were from national specialty pharmacies. The organizations were composed of a variety of types of specialty pharmacies. Most companies were independent and wholly owned, or owned by managed health plans, PBMs, or retail pharmacies. Their organizations are contracted with a total of 6,008 health plans, representing more than 720 million members.

Most respondents said their organization defines biologic drugs as all medications that are produced by means of biological processes involving recombinant DNA technology (Figure 1). The question invited respondents to check all answers that applied, and about a third of the participants selected each of the other possible replies in addition to

the majority choice. Therefore, the overall response underscores the lack of a single industry-wide definition. The term "biologic drugs," said Jason Boeshans, RPh, pharmacy director of PharmaCare Specialty Pharmacy in Portland, Oregon, "applies to a lot of different things."

Respondents reported an annual average percentage change of 9% in their organizations' pharmacy prices for the last fiscal year. "This seems about average," said Debra Thompson, RPh, manager at the Dallas branch of CVS Caremark Specialty Pharmacy in Richardson, Texas. "Most drugs go through one price change per year," added Boeshans.

One surveyed organization experienced a 30% annual change in pharmacy prices over its last fiscal year; a few saw a change of more than 20%; and two organizations experienced no change in pharmacy prices in the past fiscal year.

When office-administered injectable and infusible drugs were excluded, three-quarters of respondents said they expect prices to increase by 0% to 10% over the next 12 months (Figure 2). "This is no surprise," said Thompson.

Self-injectables and oral formulations have permitted patients to assume more responsibility for their own treatment, with the possibility that compliance may suffer.

Figure 1: How does your organization define biologic drugs?

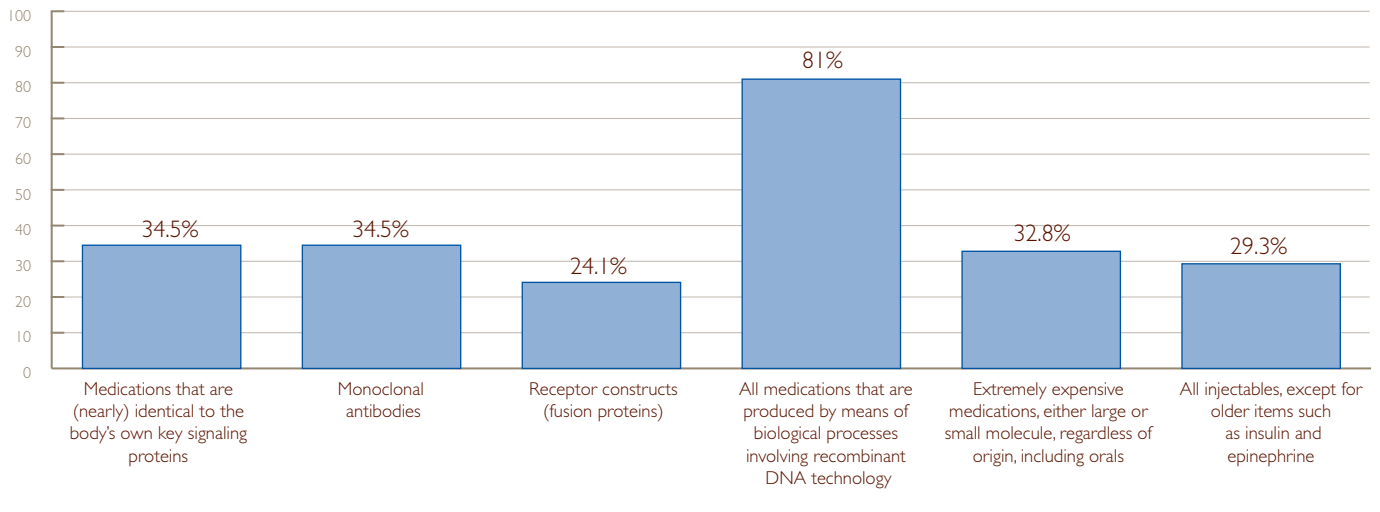
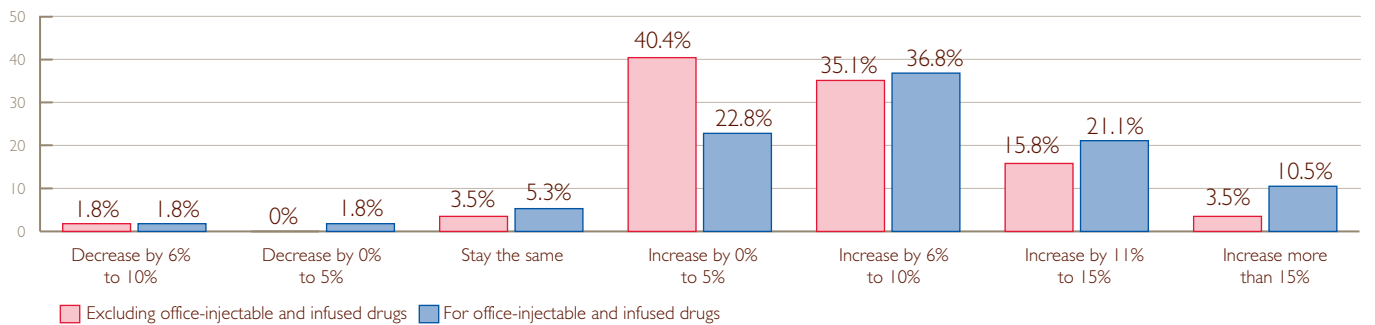


Figure 2: What is your expectation of pharmacy price trends in the next 12 months?



While Boeshans agreed with this estimate, he found it surprising that 2% of respondents projected a 6% to 10% decrease.

When physician-administered injectables and infusibles were included as part of the overall calculation, almost 60% of respondents projected an increase of 0% to 10%. But 21% said they believe pharmacy price trends will increase by 11% to 15%, and 11% project an increase of more than 15%. Many of these medications “need mixing and are associated with higher-risk categories,” explained Thompson. “They usually have a safety factor, a certain risk factor,” and are “associated with a higher-cost profile.”

Among patient services that pharmacies offer payers to support prescription management, drug utilization review was cited by 83% of respondents (Figure 3).

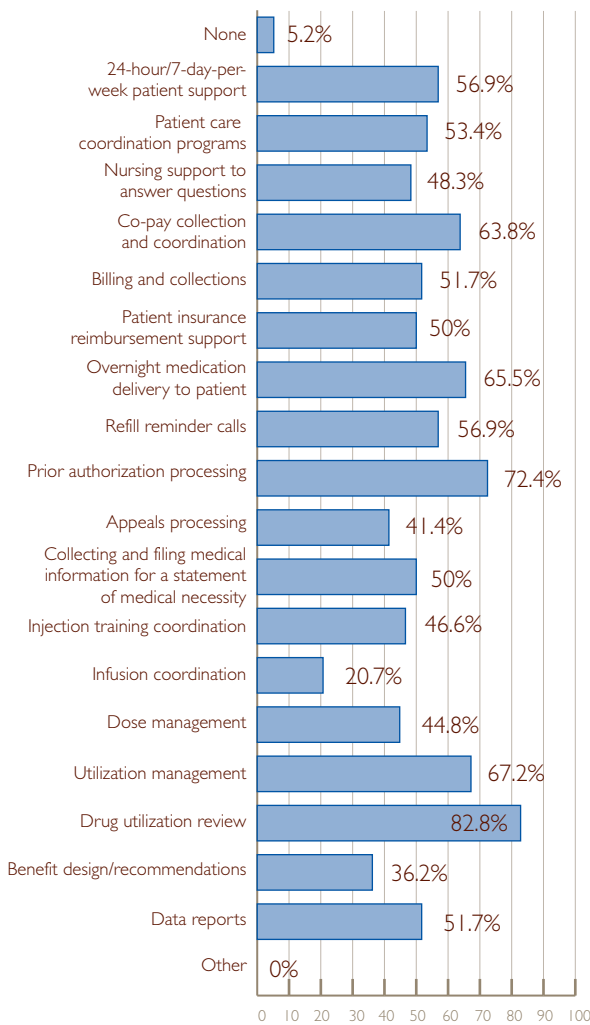
“Drug utilization review is fairly typical among specialty pharmacies as opposed to retail pharmacies,” said Boeshans. He ranked monthly refill reminders and PA processing as two other priorities. Within Caremark, Thompson said, “there are multiple utilization review and

[PA] departments.” When an insurer signs up with the company, she added, “it determines what benefits it wants included,” and it can also “determine the classes of medications and the therapies it wants reviewed.”

Most respondents ranked dose escalation of biologics as a serious cost-control issue for themselves and their contracted health plans. “Today cost control is of the utmost importance,” said Thompson. “And with more specialty agents, I don’t see the costs going down at all.” She cited RA as a good example. “Six [specialty]

Specialty pharmacies and PBMs have a role to play in synthesizing the needs of patients, physicians, health plans, and pharmaceutical manufacturers.

Figure 3: What patient services does your pharmacy offer to the payer to support prescription management?



medications are used for RA. New medications are coming out, but the costs are all high.”

Compounding the cost issue is that these therapies “are given for the patient’s lifetime,” Thompson added. Caremark, she said, dispenses four injectable multiple sclerosis therapies, and “all are extremely expensive. Patients often will start with one and then go to another, and it’s the same with RA” drugs, she said.

Sixty-seven percent of respondents indicated that their largest contracted health insurer is most concerned with managing the costs of RA. Cancer, with a 55% response rate, ranked second. Cancer is “where the biggest bulk” of costs falls for many plans, said Boeshans, who added that oral oncology drugs “will be a big area for growth.” In third place was MS, at 50%. “These drugs represent a big dollar amount. Some of the new ones are quite expensive,” added Boeshans.

Compliance and adherence issues can have a bearing on health care dollars as well. Biologic agents “all produce side effects,” said Thompson. “In some cases, the side effects make you feel worse than you did before you started on the therapy.” Her company calls patients when it’s time for their refill and communicates with physicians if the patients are missing doses.

Many RA therapies are also indicated to treat psoriasis, but only 21% of respondents said their largest contracted health plan is most concerned with managing the costs that are generated by this condition. “Psoriasis is a visible disease that could be hidden by clothes but not always. Psoriasis patients usually want to stay on the therapy because they have a visible sign of the disease,” said Thompson.

Respondents ranked a variety of utilization management strategies that are used to control the costs of biologic agents (Figure 4). These tactics are used either voluntarily or because they are mandated by health plans. PA was ranked highest, at 88%. Fifty-nine percent of respondents said they use step therapy; 57%, utilization management; 55%, dose management; and 55%, mandatory specialty pharmacy for patients. Forty-seven percent of respondents said they use patient education as a utilization management strategy for biologics, and 41% said they use individual patient assessment prior to medication shipment.

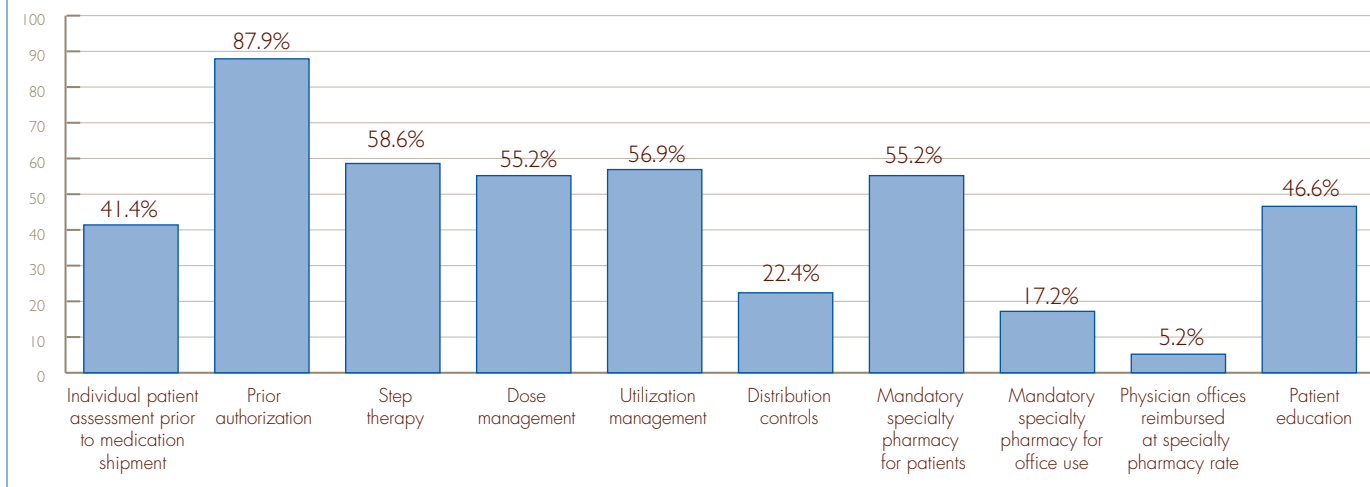
Boeshans said his plan uses most of these approaches but that he has “not heard of” reimbursing physician offices at specialty pharmacy rates, which only 5% of respondents said they use as a utilization management strategy for controlling the costs of biologic treatments.

Forty-five percent of respondents said that when a biologic agent has been approved for multiple indications, they are able to determine which disease is being treated with the agent because the information is readily available from the documentation that the organization receives. Twenty-eight percent said they can make the determination if they request a special report, and 22% said the information is not readily available.

The ability to make this determination “is a big part of specialty pharmacy,” said Boeshans, who added that the response percentages seemed low to him. Thompson agreed, noting that “with every patient we provide medication for, we need an ICD-9 code or we cannot dispense the medication.”

During the PA process the diagnosis code, which assists with verifying the dosing, also is required, Thompson said. As an example, she pointed to adalimumab (Humira®), which has multiple indications. “The dosing varies with the diagnosis,” she noted.

Figure 4: What utilization management techniques do you use, either voluntarily or because they are mandated by health plans, to control the cost of biologics?



Forty-five percent of respondents said that following the initial decision to approve or deny use of a biologic, their organization takes two to three days to inform the clinician of the decision. One-fifth give same-day notification, and 10% tell the physician in less than a week. “These numbers look fairly typical,” said Boeshans, whose organization usually takes two to three days to inform the clinician. When PharmaCare gets a referral, he said, it submits all of the information to the plan, and then it’s “a matter of waiting for the health plan to get back to us.”

Three percent of the surveyed organizations give notification in less than two weeks, and 2%, in less than a month.

Caremark, said Thompson, generally informs the physician within 24 hours. She was surprised that 14% of the respondents said their organization does not make or communicate a decision in regard to approving or denying the use of a biologic. When such a decision falls to plans to make, “they need a department that does its own PA and guidelines management,” she said.

Respondents reported an 18% average rate for initial denials of properly filed PA requests for biologic agents. To Boeshans, this “seems a little high”; he thought 10% would be a more likely rate. The primary reason for initial denials, he said, is that patients “don’t meet medical criteria, such as trying and failing a previous therapy.” Respondents indicated that 32% of the agents that are initially denied are ultimately approved.

Thompson, however, was surprised that both the initial denial rate and the subsequent approval rate were as low as they were in the survey. Caremark, she said, sees a 20% to 30% initial denial rate, and 40% to 50% of those denials are ultimately approved.

Getting specialty pharmaceuticals to patients when they need them is critical for many conditions, so pharmacies need to be nimble and flexible in their distribution methods (Figure 5). Sixty-four percent of respondents said they use overnight delivery. Half of the respondents’ organizations use mail order, and slightly less than half use an affiliated retail pharmacy. Thompson indicated that Caremark is in the development stage with CVS to use an affiliated retail pharmacy, but the organization “does not have the ability today.”

Given the importance of patient compliance with specialty therapies, many plans and physicians depend on specialty pharmacies not just to answer patients’ questions but also to maintain contact with patients. Most respondents indicated that they have monthly contact with CD and RA patients.

“This is expected,” maintained Thompson. “The goal is to dispense either a one-month or three-month supply,

Figure 5: What distribution methods does your pharmacy utilize to fulfill patient medication?

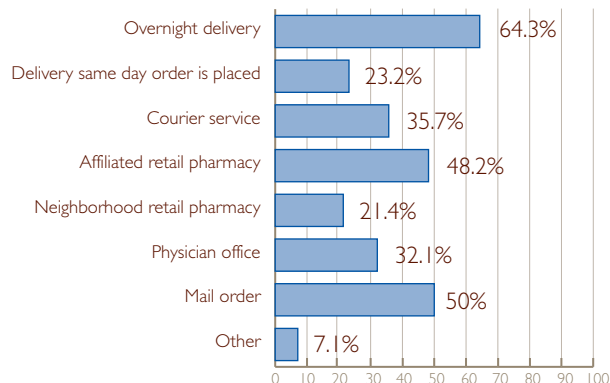
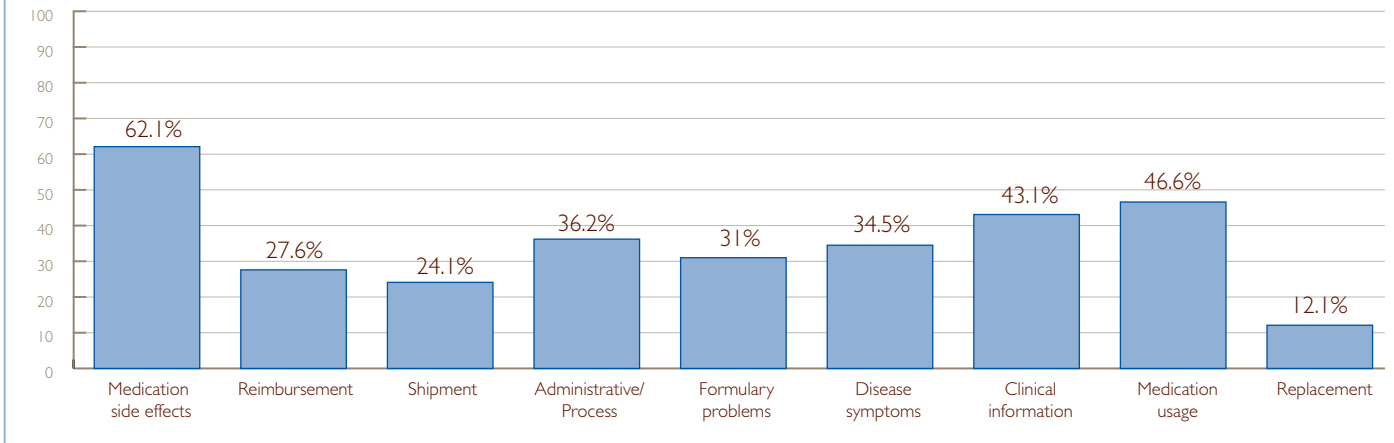


Figure 6: What issues arise most frequently during contacts with CD patients?



and we speak with patients one time per month” when therapy is initiated. “Once patients have started on therapy and are stable, we speak with them as often as their prescription is refilled,” she said.

Boeshans and Thompson both expressed surprise that 11% of respondents said they speak with Crohn’s patients once every few days and 13% do the same for RA patients. “I’m not sure why pharmacies would contact these individuals so often,” Boeshans said, unless, he added, they are new patients.

Fifty-nine percent of respondents said that overall, the frequency of contact for CD is about the same as for other chronic degenerative diseases. Sixty-eight percent of respondents said that overall, they contact RA patients about as frequently as they contact patients with other chronic degenerative diseases. With a CD or RA diagnosis, said Thompson, “we almost always dispense the prescription to the patient’s home.” Infusible therapies such as infliximab (Remicade®) and abatacept (Orencia®) are shipped to the physician’s office.

Sixty-two percent of respondents said the topic that arises most frequently during their contacts with CD patients is medication side effects (Figure 6). Forty-seven percent cited medication usage as the second most frequently discussed topic, and 43% cited clinical information. For patients with RA, 60% of respondents selected side effects as the most frequently discussed topic; 48% cited medication usage; and 43% cited clinical information (Figure 7).

Both sets of results “look quite normal,” said Boeshans. Crohn’s medication in particular, he said, “has lots of side effects

— regardless of the particular treatment — that are disease-specific.”

Specialty pharmacies and PBMs provide an array of reimbursement support services for patients treated with biologic therapies. Almost 60% of respondents said they help patients meet PA requirements. Forty-five percent coordinate benefits from multiple payers, and 45% help patients qualify for benefits sponsored by manufacturers or government agencies.

Specialty pharmacies provide services not only to patients, but also to pharmaceutical manufacturers (Figure 8). More than half (56%) of the respondents said they provide clinical management programs, and 41% provide data reports. Boeshans questioned how often specialty pharmacies would assist with benefit investigation (17%) and appeal processes (24%). Twenty-two percent of respondents said they provide dedicated account management, and Boeshans suggested that these services may be employed in signing patients up for risk-management or adherence programs when manufacturers offer them.

Thirty-nine percent of respondents said they make refill reminder calls, and Boeshans believes that many pharmacies probably make these calls as part of their contracts with payers. Nearly 40% of respondents said they provide co-pay processing and coordination services to manufacturers. This percentage “seems a little high,” said Boeshans. “I’m not sure what manufacturer would have to do this,” he added. Clinical trial conversion programs, which 9% of respondents said they provide, “seem like a good idea,” he said.

“Compounding the cost issue for biologic therapies is that they “are given for the patient’s lifetime.”
—Debra A. Thompson, RPh, Dallas branch manager for CVS-Caremark Specialty Pharmacy

Figure 7: What issues arise most frequently during contacts with RA patients?

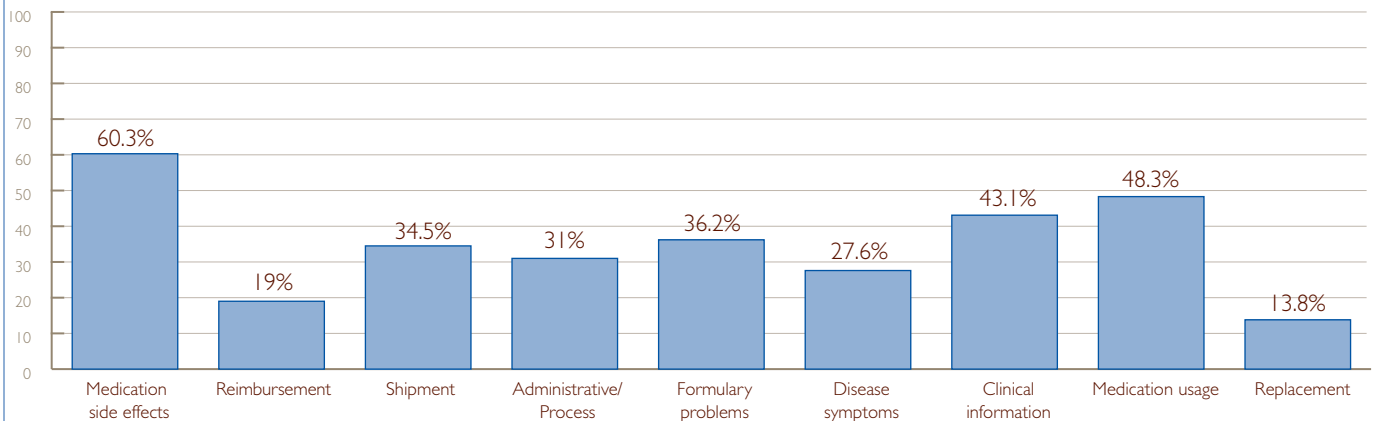
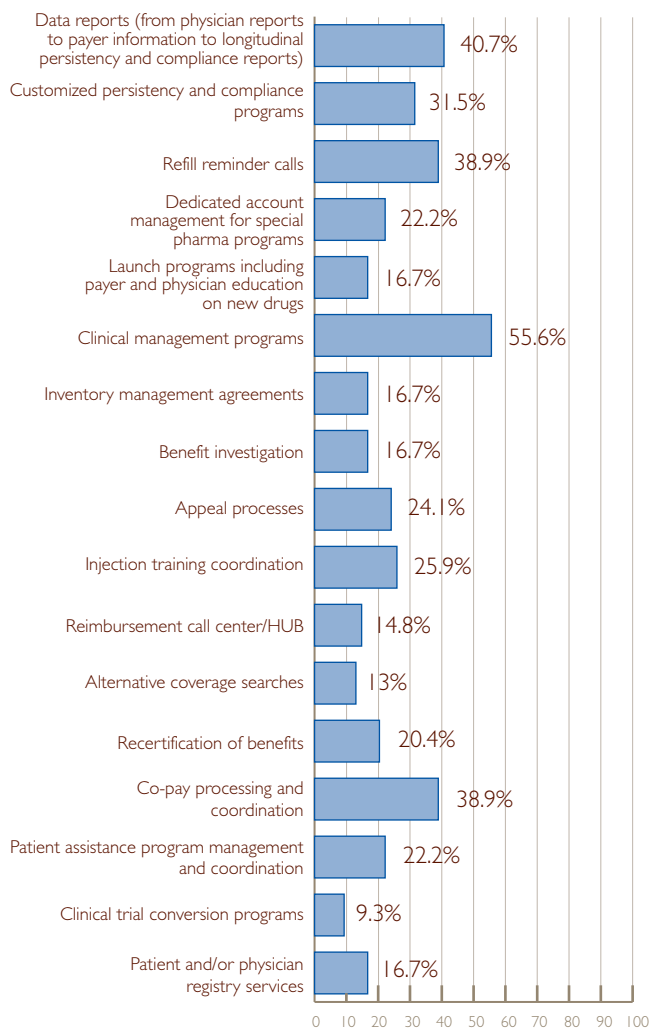


Figure 8: What specialty pharmacy services does your organization provide to pharmaceutical manufacturers?



Various approaches in regard to pricing can help mitigate rising costs to a certain extent. Twenty-eight percent of respondents said they contract directly with manufacturers

for drug pricing, and 35% said they contract with these companies for drug rebates.

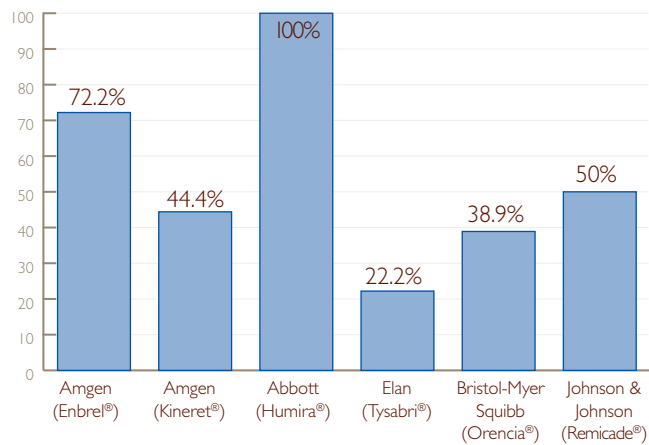
All of the specialty pharmacies that contract directly with manufacturers said they work with Abbott in regard to Humira (Figure 9). Seventy-two percent said they contract directly with Amgen in regard to Enbrel®. Half of the respondents said they contract with Johnson & Johnson for Remicade. Boeshans suggested that some of the treatments that received a smaller response may be administered by infusion in physicians' offices.

Specialty pharmacies are often in touch with plans, physicians, and patients. As a result, these constituencies depend on specialty pharmacies to enhance delivery of care. Eighty-nine percent of gastroenterologists and rheumatologists agreed that specialty pharmacies can add value to physicians' delivery of care for CD and RA patients. Boeshans said he is not sure why 10% of respondents disagreed with this view, unless they perceive specialty pharmacies solely as distributors that provide specialty drugs.

Respondents indicated that specialty pharmacies add value in the following ways: dosing in unique patients (100% of gastroenterologists and 91% of rheumatologists agreed); assisting with insurance billing and reimbursement (95% and 97%, respectively); changing patient care (97% and 94%); augmenting patient education (93% and 98%); changing the type of medication prescribed (89% and 96%); and changing the way in which medication is prescribed (94% and 88%).

Sixty-nine percent of respondents either agreed or strongly agreed with the statement that biologic agents have an appropriate risk-benefit ratio for the treatment of mild-to-moderate inflammatory diseases; 23% expressed a neutral response to the statement (Figure 10). Ninety percent agreed or strongly agreed that biologic agents

Figure 9: If your answer was yes to either pricing or rebates, which manufacturer(s) do you contract with directly?

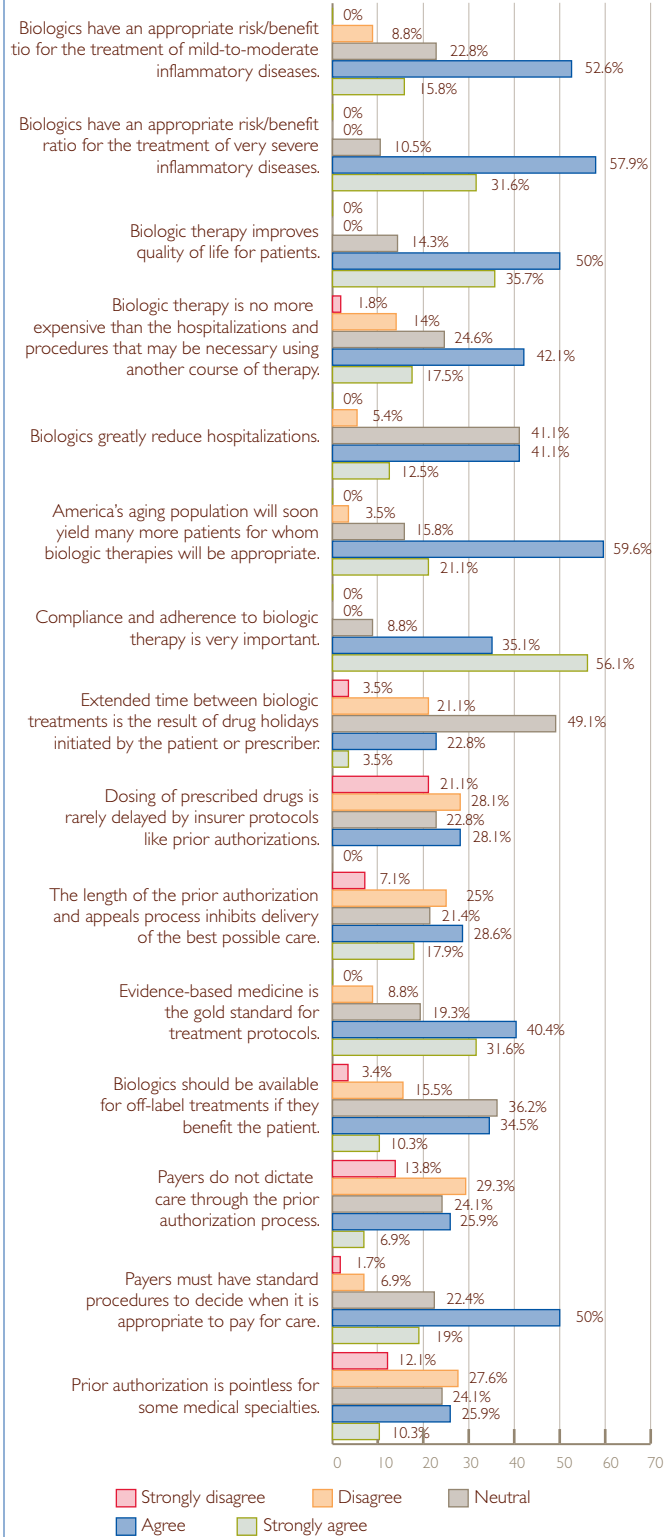


have an appropriate risk-benefit ratio for the treatment of very severe inflammatory diseases; 11% were neutral in regard to this statement. Eighty-six percent agreed or strongly agreed that biologic therapy improves patients' quality of life. Fourteen percent of respondents expressed a neutral response to this statement, most likely, according to Boeshans, because of the "few patients who don't get much benefit" from biologic agents.

Eighty-one percent of respondents agreed or strongly agreed with the statement that America's aging population will soon yield many more patients for whom biologic therapies will be appropriate. "I agree with this view, especially in regard to oncology," said Boeshans, adding that while RA will impact an older demographic as well, CD does not necessarily have the same demographic profile.

Forty-nine percent of respondents disagreed or strongly disagreed with the statement that dosing of prescribed drugs is rarely delayed by insurer protocols like prior authorization; 23% were neutral; and 28% agreed or strongly agreed. Thirty-two percent of respondents disagreed or strongly disagreed with the statement that the length of the PA and appeals process inhibits delivery of the best possible care; 21% were neutral; and 47% agreed or strongly agreed. "If payers are on top of the process, it shouldn't be delayed too much," said Boeshans. "It would be nice if everything happened without problems. But the process is usually pretty quick."

Figure 10: Please share your opinion on the following statements.



Gastroenterologists



Crohn's disease is an autoimmune inflammatory bowel disease (IBD) that affects the lining of the digestive tract. The predominant symptoms are abdominal pain, diarrhea, cramping, and bloody stools. Symptoms vary among patients, may change with time, and range in severity. About half of all CD patients have relatively mild symptoms.^{1,2} Severe cases can be debilitating and may disrupt routine activities such as work and school. CD also increases the risk of colon cancer.

Ulcerative colitis (UC), an IBD that is related to CD, can cause similar symptoms, which can make a definitive diagnosis difficult. But while UC is limited to the colon, CD may involve any part of the gastrointestinal (GI) tract from the mouth to the anus.

The onset of CD can occur gradually or suddenly at nearly any age. Most patients are diagnosed between the ages of 15 and 35, and prevalence of the disease is equal among women and men. Of the estimated 500,000 Americans who have CD, 10% are under age 18.^{3,4}

Significant GI complications frequently develop in the presence of CD, including intestinal ulcers, fistulas, reduced appetite, fever, fatigue, weight loss, and malnutrition. Complications beyond the GI tract may also arise, including arthritis, inflammation of the eye, skin disorders, and kidney stones. In children, the disease can stunt growth and delay sexual development.

Complicating the evaluation and management of patients with CD is its unpredictability. Patients may be symptom-free for extended periods or may experience recurrent symptomatic episodes. Symptoms may flare up unexpectedly or may disappear entirely for months or even years.

The trigger for CD remains unknown, though experts agree that it involves an abnormal cell-mediated immune response to bacterial flora in the digestive tract. Some

researchers suspect that the culprit is viral or bacterial.⁵ Heredity also plays a part: about 20% of people with CD have a parent, sibling, or child who has the disease.^{1,2}

There is no cure for CD, so the best that can be expected from medical therapy is the induction and maintenance of clinical remission with minimal adverse drug effects.

The standard course of treatment for CD is the step-up approach, which begins with anti-inflammatory medications (e.g., sulfasalazine and mesalamine), followed sequentially by more potent — and often more toxic — drugs when response is insufficient or side effects become intolerable. Corticosteroids (e.g., prednisone), which may come next, are often effective for reducing Crohn's-related inflammation, but they can generate severe side effects and drug dependence. Because of these risks, steroids are typically used for fast, short-term relief of symptoms.

Immunosuppressants (e.g., azathioprine and 6-mercaptopurine) are frequently the next step up the treatment ladder. Clinicians usually reserve more potent immunosuppressants (e.g., methotrexate and cyclosporine) for patients who are unresponsive to other medications.

The newest additions to the CD drug regimen are biologic agents that are designed to repair the immune system. Four are FDA-approved for treating CD patients: infliximab (Remicade®), adalimumab (Humira®), certolizumab

pegol (Cimzia®), and natalizumab (Tysabri®).^{*} All four are monoclonal antibodies. The first three inhibit tumor necrosis factor (TNF), while Tysabri inhibits inflammatory integrins from binding to intestinal wall cells. (Anti-TNF drugs were initially used to treat patients with RA.)

Anti-TNF agents have generated much interest among gastroenterologists, a growing number of whom are using them regularly. Response rates cited in clinical studies are high. Research has shown that anti-TNF agents induce and maintain remission of CD more effectively than other

“More than nine out of 10 gastroenterologists surveyed said they use biologic agents to treat CD patients.”

^{*} Please see Cimzia's® important safety information on page 49 and accompanying full prescribing information.

drugs do. About three out of four people who now have CD eventually undergo at least one surgical procedure.

Cost is a factor, however. Some anti-TNF therapies top out at more than \$20,000 annually, and some clinicians have wrestled with insurance companies to obtain timely authorization for the use of these treatments.

To gauge current thinking about the use of biologic agents for treating patients with CD, the *Biologics Trend Report* surveyed gastroenterologists in practice settings around the United States. More than half of the 121 respondents have practiced gastroenterology for more than 15 years; more than a third of the respondents have practiced for less than 10 years. A third of the respondents are in solo practice; a third work in a single-specialty clinic; 15% practice in a multispecialty clinic; and 15% practice in an academic clinic or hospital. The average practice among respondents serves 5,700 patients.

As a group, respondents seemed confident of their ability to manage their CD patients: half listed themselves as CD specialists, although a fifth said they refer patients with severe symptoms to a specialist. A total of 14% of patients in the care of all the survey respondents have CD.

More than nine out of 10 respondents said they use biologic agents to treat CD patients — an unmistakable signal that these treatments have become a mainstream therapy option, though one whose full impact remains to be understood. Survey responses indicated a belief that the number of patients with CD who are treated with anti-TNF drugs or other biologics will increase dramatically in years to come. More than three-quarters of respondents said they had written more prescriptions for biologics over the past year than during the preceding year; while only one in 10 had written fewer prescriptions (Figure 1). Nearly 80% anticipate that they will write even more prescriptions for biologic agents over the next year (Figure 2).

Remicade is now the most widely used anti-TNF drug for CD. According to the survey data, twice as many patients with moderate-to-severe CD are treated with Remicade than with Humira. The wide margin may be related to an earlier FDA approval date: Remicade received FDA approval for CD in 1998; Humira received approval in 2007; and the two other biologic agents received approval in 2008.

Michael Samach, MD, a gastroenterologist at a single-specialty clinic in Morristown, New Jersey, predicts that Humira use will almost certainly rise, in large part because patients can self-inject the drug. The convenience of

Figure 1: Have you written more prescriptions for biologics during the past 12 months than in the preceding 12 months?

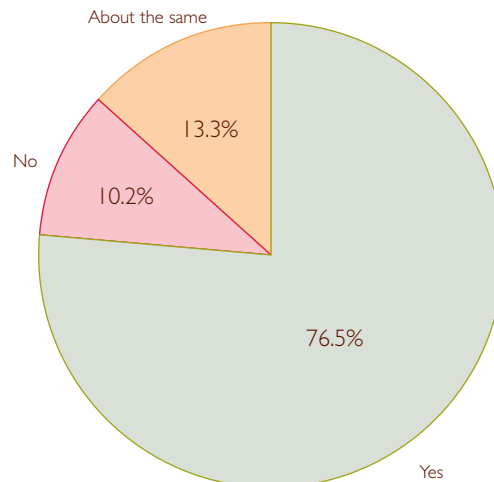
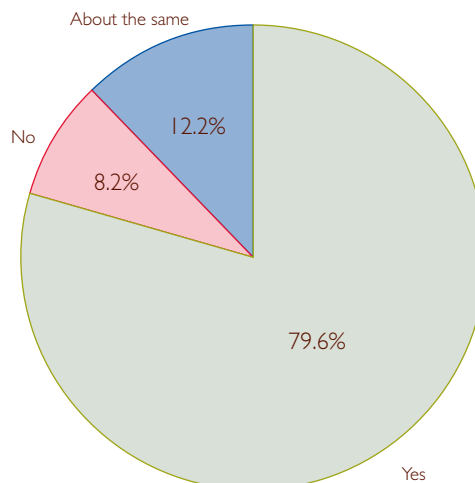


Figure 2: Do you anticipate increasing the number of prescriptions you will write for biologics next year?



administering Humira contrasts with administration of Remicade, which requires periodic, time-consuming infusions at a clinic. Jay Zelinsky, MD, a solo-practice gastroenterologist in Bayonne, New Jersey, says that younger people in particular are attracted by the freedom that Humira permits, though the choice of treatment is contingent on drug efficacy (see sidebar "Crohn's Top-Down: Two Views," on page 33).

Therapy failure and the presence of severe or refractive disease were the most compelling reasons that respondents considered in deciding which patients are candidates for biologic agents (Figure 3).

Figure 4 breaks out factors taken into account when clinicians are deciding whether to use biologic therapy. Severity of disease tops the list by a substantial margin.

Respondents rated factors they consider when evaluating patients' responses to therapy.

- I always use the full Crohn's disease activity index (CDAI) 12%
- I use most of the factors 32%
- A drop in CDAI of 100 points or more 8%
- Mucosal healing 51%
- No fistulae visible 44%
- Clinical remission 83%
- Improvement in the patient's ability to function in daily life 75%

Respondents cited treatment failure as the primary reason for halting biologic therapy. Treatment failure outpaced adverse drug reactions by almost 2 to 1 (Figure 5).

Though the influence of health insurers comes into play, lack of response was the main reason clinicians gave for switching patients to a different anti-TNF agent (Figure 6). Twenty-seven percent of clinicians said patients responded better to the second drug; 22% said patients responded the same to the second treatment; and 24% indicated that patients responded less well to the second drug than to the previous treatment.

Clinicians were asked how insurance companies affect their use of biologic agents. For some, the degree of that influence is substantial, often requiring clinicians to hire office personnel to deal with insurance-related issues; in

Figure 4: Please rate the importance of the following factors when considering whether to recommend a biologic agent versus conventional therapy for a patient.

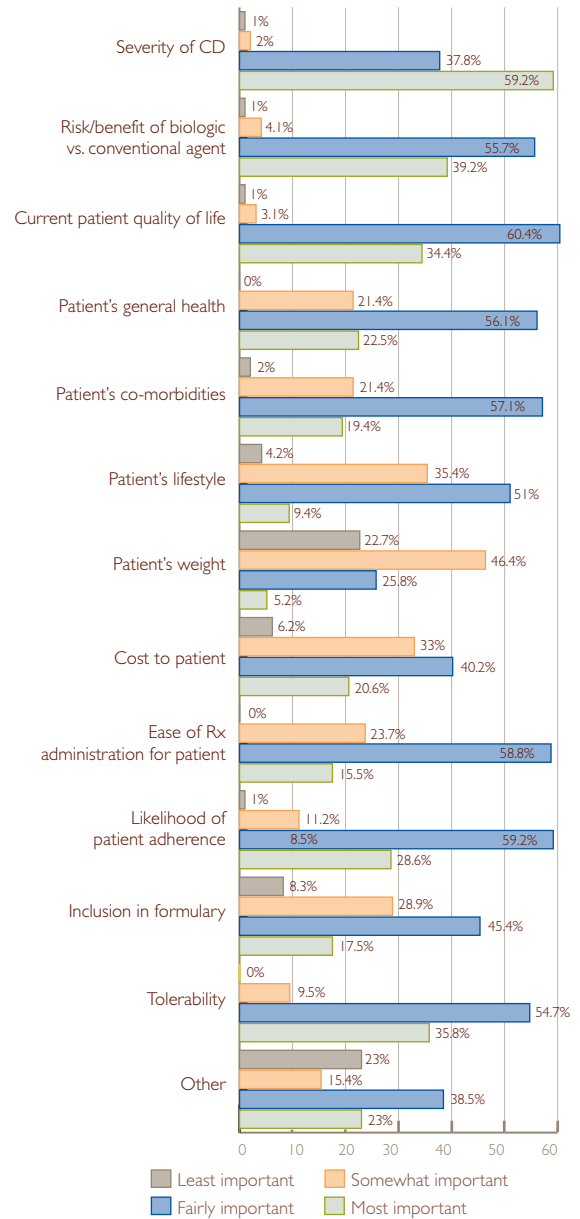


Figure 3: Who should receive biologic therapy?

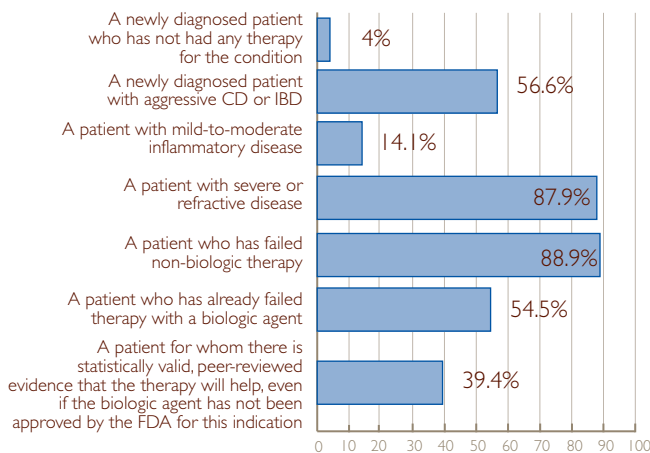


Figure 5: At what point do you halt biologic therapy?

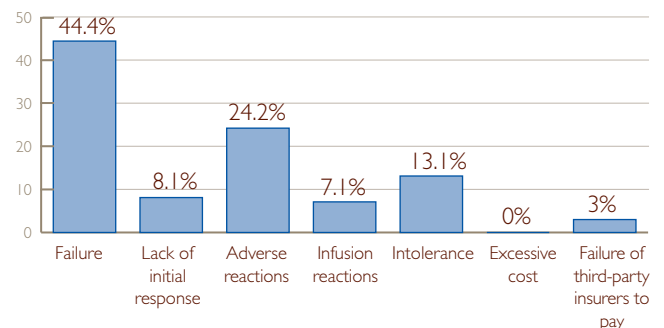
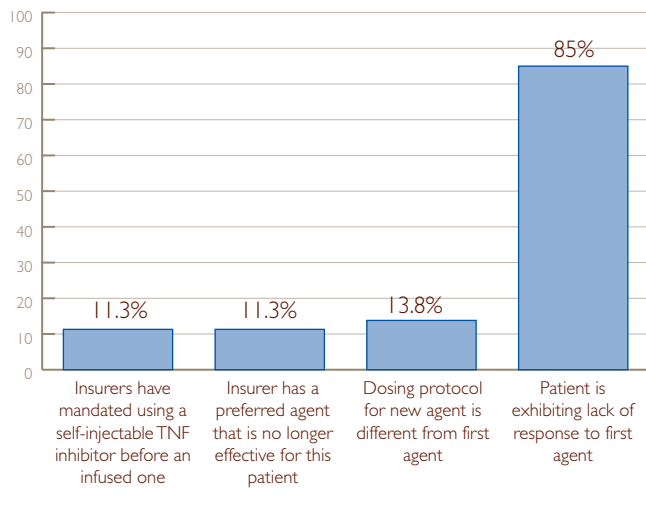


Figure 6: If your patients have switched between anti-TNF agents, what is the usual reason?



turn, the extra staffing has a direct impact on the office bottom line. Some physicians handle prior authorization themselves (Figure 7).

Respondents indicated that staff members who deal directly with insurers spend more than a quarter of their time on phone calls about drug authorizations. Nearly 40% of respondents said they have hired — and another 12% plan to hire — additional staff to handle payments and access-to-care-issues, including prior authorization for drugs.

When asked how frequently insurers try to restrict the use of biologics, respondents reported varied experiences (Figure 8). However, when problems do arise, they can have a tremendous negative impact on quality of care (see sidebar “Insurer Authorization of Biologic Drugs for

Figure 7: Who on your staff has the primary responsibility for obtaining prior authorizations and approvals for biologics from insurers?

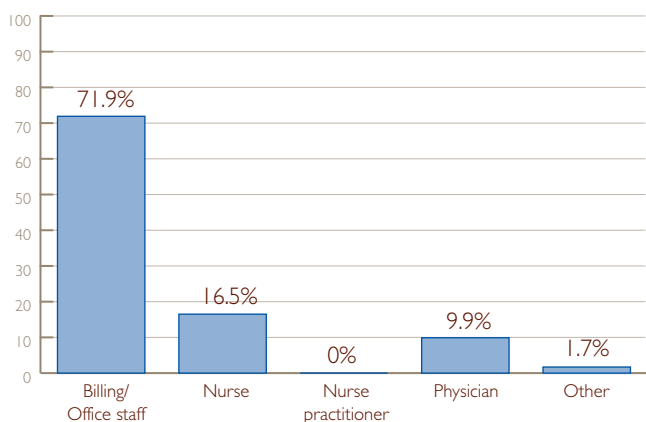
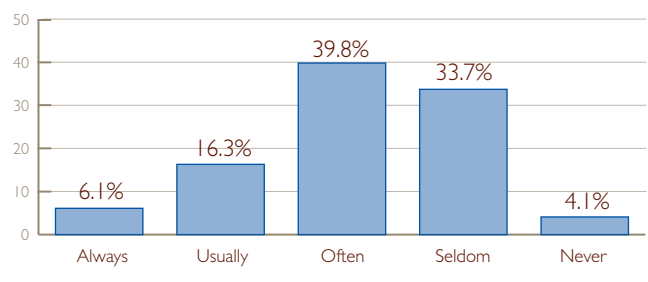


Figure 8: How frequently do insurers try to restrict the use of biologics?



Crohn’s,” on page 34).

The chief reasons insurers gave for restricting the use of biologics are as follows:

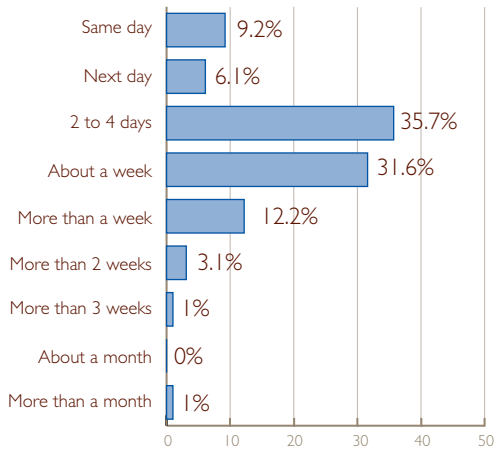
- Prior authorization before therapy starts 89%
- Formulary restrictions 54%
- Annual authorization (even if a patient was on biologics previously) 42%
- Prior authorization of dose increases 27%

Clinicians reported that the length of time they have to wait for a reply from insurers on a preauthorization request ranges from less than a day to more than a month. About two-thirds of respondents said they have to wait between two days and a week (Figure 9).

When treatment with a biologic agent is denied, 35% of respondents said they appeal but postpone the start of treatment; 52% use other drugs while an appeal is adjudicated; and 13% turn to other therapeutic agents and do not pursue an appeal.

Sixty-four percent of survey respondents agreed or strongly agreed with the statement “Biologics greatly reduce hospitalizations,” while only 6% disagreed or strongly disagreed with the statement. Belief in the efficacy of biologic agents — specifically, anti-TNF agents — is one reason that some clinicians are frustrated when insurance companies balk at authorizing their use. While they are expensive, these agents are likely to save insurer dollars in the long run by precluding hospitalization and more costly treatments (Figure 10). More than half (55%) of the respondents said that delays in the preauthorization and appeals process inhibit their ability to offer patients the best care, and 81% indicated their belief that biologic therapy improves quality of life for CD patients. These numbers highlight the tension between providers and insurers.

Figure 9: How many days does it generally take to receive an answer from insurers on a prior authorization request?



Respondents indicated positive attitudes toward patient support programs that are offered by the manufacturers of biologic agents, specifically Remicade and Humira. These programs offer patients financial aid, ongoing counseling, and training on proper use of the drugs. Fifty-six percent of respondents rated Remicade patient support programs as very good or excellent, and 55% rated Humira patient support programs as very good or excellent. The most valuable services offered, respondents said, are patient reimbursement assistance and patient co-pay rebates. Other high-ranking patient support services were education programs on disease and treatments, reminders and compliance help, medical supplies, and the availability of nurses to answer questions.

Interest levels in top-down therapy are high. Only a small proportion of respondents said they would not try this treatment strategy (Figure 11). Fifty-seven percent of respondents still said they do not think the top-down strategy for biologics will soon be widely adopted in the United States, while 43% predicted that it will be.

Clinicians are less optimistic about how insurers will respond. Many fear that authorizations will be denied for biologic agents even when their use is medically necessary. The statement top down therapy will soon be recognized as an acceptable treatment regimen by insurers received a split opinion: 28% of clinicians agreed or strongly agreed, while 26% disagreed or strongly disagreed. About half were uncertain.

Figure 10: Please share your opinion on the following statements.

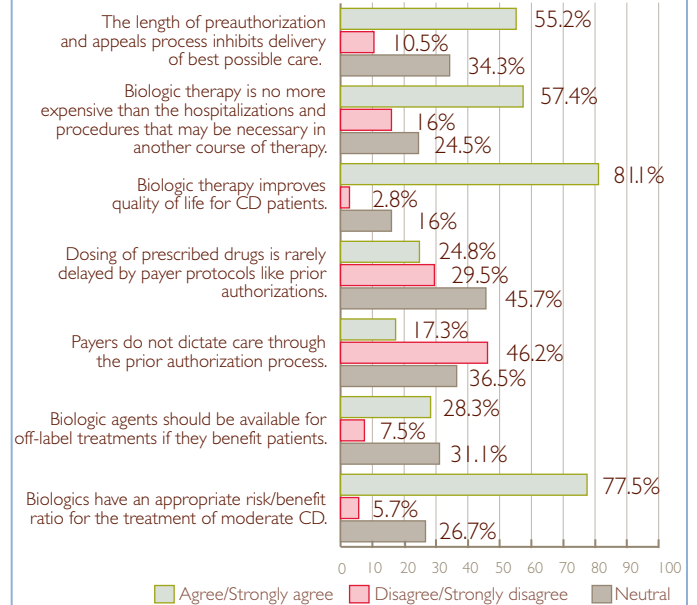
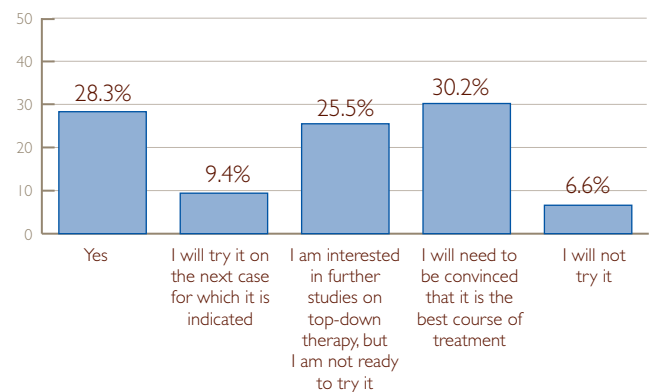


Figure 11: Have you tried top-down therapy yet?



Respondents indicated an interest in new biologic agents, including those still in the pipeline. When asked which drugs they thought will prove most valuable for patients with CD, 82% said Cimzia; 64%, Tysabri; 28%, etanercept (Enbrel®); 24%, visilizumab (Nuvion®); and 21%, efalizumab (Raptiva®).

Crohn's Top-Down: Two Views

Two gastroenterologists, each in practice for about 30 years, weigh in on biologic therapy for CD and their experience with insurers.

The Comments of Michael Samach, MD Morristown, New Jersey Single-Specialty Clinic

The number of prescriptions I write for biologics is definitely on the rise. I expect that trend to continue. I also expect that Remicade use will go down as physicians begin to try the newer biologics for patients with IBD, particularly Humira. Some physicians in our practice are now prescribing Humira. It is self-injected, and patients like the convenience. But if a patient is doing well on Remicade, there's no reason to switch him or her. I am using Humira more with new patients.

I've become significantly more aggressive in my own treatment approach than I was two or three years ago. One reason for the change is that I'm always leery of steroids. I've seen so many steroid-related problems, including too many patients who, once started on steroids, can't get off them.

The Comments of Jay Zelinsky, MD Bayonne, New Jersey Solo Practice

I rarely start off with a biologic agent for patients with a new diagnosis, and I don't really agree with the theory of top-down therapy for Crohn's patients. A patient with newly diagnosed CD who has not had any other type of therapy is not a candidate for biologics. If a patient is critically ill, I'll go with biologics, but if I can control symptoms with immunomodulators and mesalamine, I believe that's the way to go.

At the same time, the number of prescriptions I've written for biologics has gone up tremendously. Although much of the increased use in general is the result of intense marketing from the drug makers, it's also true that there are a lot more patients with CD. In addition, those who previously maintained on immunomodulators or mesalamine compounds are breaking through. Then you have no choice — you have to go with a biologic.

The insurance situation for biologics is horrible. I've had to give patients steroids multiple times because of delays,

The immunomodulators take three to four months to work, while the average response time for biologics is about six weeks, and often there's a response after the first dose.

The use of top-down therapy is increasing. If you survey gastroenterologists a year from now, you will see a reversal in the numbers. There will be more who think top-down therapy will be widely adopted as the first course of treatment.

I haven't had to make any drastic changes in treatment because of medication denials from insurance companies. Once we get prior authorization, the process usually works, and it takes one to four days from the time of the authorization request to approval. However, I can see how denials could occur for biologics, even though I haven't had a real problem with them.

and multiple times I've had to hospitalize them, and then the insurer has to pay substantially more than if they had allowed the drug sooner.

To submit an approval can take hours, days, and multiple phone calls over weeks. It usually takes at least four or five phone calls. I spend hours and hours on the phone for all kinds of insurance nonsense. Insurers always restrict the use of biologics. They request prior authorization every single time, always for dose increases, and then they need another prior authorization every six months. If I want to start a patient on Humira and it's not on formulary, I have to use Remicade. A patient must fail therapy first before he or she can get the non-formulary biologic.

On average it takes at least two weeks or more until I can dispense the drugs. Denial of biologic therapy is really a problem. I've had to write letters and have threatened to sue an insurer. In cases where patients really needed the medication, they got it sooner or later, but at times I've had to speak with the director of the insurance company.



Insurer Authorization of Biologic Drugs for Crohn's

**The Comments of Beth-Ann Norton, MS, RN, CS
Massachusetts General Hospital, Boston**

Beth-Ann Norton, a nurse practitioner at Massachusetts General Hospital, describes two battles she waged with insurance companies to obtain authorization of biologic agents for patients with CD.

We had a young woman on Remicade who lost her response to that agent, and we wanted to put her on Humira, which is FDA-approved for CD and has become a standard treatment for CD. But the insurance company kept stalling. They asked for more chart information, more paperwork, more medical records, reviews, and letters of medical necessity. Every time I picked up the phone, I spoke with a different person.

Finally, after several days, I found someone to help me through the process, but it still took three-and-a-half weeks to get the medication, and the patient suffered badly. She had to be on prednisone, which has a very bad side-effect profile. If we had gotten the proper drug authorized in a timely manner, she would have been spared a lot of pain and would have been able to avoid corticosteroids.

Insurance companies frequently delay the process because the medications are expensive. I try to explain

to them that without the drugs, the patients will get sicker and might need to be hospitalized. This has happened. Then the insurer is faced with an expense that exceeds the cost of the drug they should have approved in the first place.

In another case, a young man with a particularly bad case of CD had to undergo multiple surgeries. He can't have any more surgeries because he now has short bowel syndrome after all those procedures. We wanted to give him Humira and told the insurance company that without it he would not be able to absorb food and would need total parenteral nutrition, which is labor-intensive and costs \$1,000 per bag. No matter how many letters I sent them, they just said no. The reason they gave was that the dose frequency we wanted had not been approved, even though it had been approved. Eventually I got approval, and the patient is responding, but he suffered unnecessarily.

This problem is only getting worse. The insurance people are so isolated in their ivory towers. They don't have to deal directly with sick people. It should be up to physicians to say which of these drugs should be used and when.

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 - ² Crohn's & Colitis Foundation of America. Living with Crohn's disease. Available at: <http://www.cdfa.org/frameviewer?url=/media/pdf/crohns2005.pdf>. Accessed July 19, 2008.
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 - ⁴ Loftus EV, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America. *Alimentary Pharmacology & Therapeutics*. 2002;16:51-60.
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Rheumatologists



Rheumatoid arthritis is a chronic joint disease that affects an estimated 1.5 million Americans.¹ In people with RA, the body's immune system turns its attack against the thin membrane that lines the joints, leading to joint pain and inflammation. If not checked, pain and stiffness can interfere with daily life, and inflammation can eventually lead to irreparable joint damage and disability.

Traditionally, treatment for RA consisted of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin[®], Advil[®], and Nuprin[®]) and naproxen (Naprosyn[®] and Naprelan[®]) to ease pain and inflammation; corticosteroids to halt inflammation; and disease-modifying anti-rheumatic drugs (DMARDs). Yet such treatments can carry dangerous side effects and often have little effect against debilitating joint damage.

In the past decade, the class of genetically engineered drugs referred to as biologic agents has changed the course of RA for many patients. Infused or injected, these drugs target components of the aberrant immune response to control RA and prevent the damage it incurs. Many people with RA who take biologics respond favorably to them.² Most RA patients who are treated with biologics experience a remission of their disease.

Six biologic agents have been approved by the FDA for RA, and more are in development.³ One of the agents in development, tocilizumab (Actemra), is currently under review by the FDA. Several biologic agents have also been approved for other inflammatory joint diseases, including ankylosing spondylitis, in which inflammation causes stiffening and fusing of the spine, and psoriatic arthritis, an inflammatory form of arthritis that is accompanied by the scaling skin disease psoriasis.

Of the 98 rheumatologists who responded to the survey, most are in mid-career or in the later years of their career; 24% have been in practice more than 20 years; and 15% have been in practice less than five years (Figure 1). More than one-third of the respondents (38%) work

in multispecialty clinics; more than one-quarter of the respondents (27%) work in single-specialty clinics. Seven percent practice in an academic clinic or a hospital (Figure 2). Respondents indicated that they work on average just over 49 hours per week.

"These are people with their nose to the grindstone," said Jack Waxman, MD, a survey participant who practices rheumatology in Santa Rosa, California. "These are the doctors who are out there dealing with patients day to day. These are the front-line rheumatologists."

All of the physicians who responded to the survey prescribe biologic agents. Though a significant drawback with these new agents is their cost, most respondents indicated that they will continue to prescribe them. Eighty percent (Figure 3) said they anticipate increasing the number of prescriptions they will write for biologics next year. More than 75% of respondents said they have written more prescriptions

for biologics during the past 12 months than during the preceding 12 months.

“
Eighty percent of surveyed rheumatologists said they anticipate increasing the number of prescriptions they will write for biologics in the coming year.
”

Figure 1: How many years have you been practicing rheumatology?

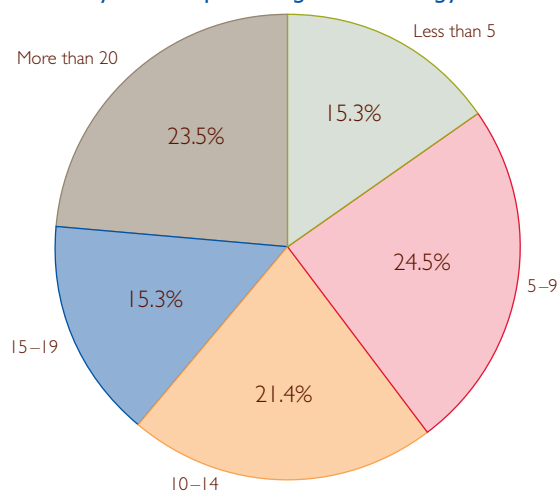
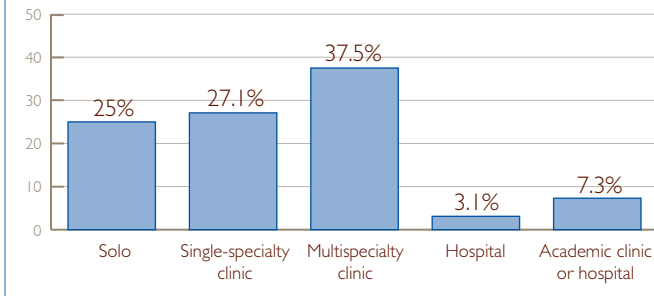


Figure 2: Which choice best describes your practice environment?



“Doctors have realized that these are really good drugs. They are willing to spend some time themselves getting approval for them or hiring people to get the approval,” said Waxman. “Even though it means taking on a fight with insurance companies, physicians are recognizing that patients do so well on these drugs that they are willing to put up with the hassles and go ahead with the treatment.”

Respondents said they spend the great majority of their time (87%) seeing patients and dealing with clinical issues. On average 6% of their time, respondents said, is devoted to helping patients access care, which includes obtaining authorizations and filing appeals (Figure 4). Half of the respondents said billing and office staff members have primary responsibility for obtaining prior authorization and approval from insurers; 40% said a nurse takes care of these tasks; and 7% said they themselves are primarily responsible for obtaining prior authorization and approval from health plans (Figure 5). David I. Weiss, MD, a survey participant and rheumatologist who practices in Hattiesburg, Mississippi, noted that even in practices where the office staff “tends to do the bulk of it,” physicians “still have to spend a certain amount of time in the appeals process. This may involve generating letters, reviewing charts, discussing matters with the patient, and providing the patient with needed information. At least I do that,” he added.

Respondents reported that when office staff members bear the primary responsibility for interacting with insurers, 45% of the staff members’ time is devoted to calls about insurance-related drug approval. Forty percent of clinicians said they have had to hire additional staff to handle payments and access to care, and 12% said they are planning to hire additional staff within the next year.

The average number of patients that physicians reported having in their practice was 2,340. Of those, an average of approximately one-third had RA, ankylosing spondylitis, or psoriatic arthritis.

Figure 3: Do you anticipate increasing the number of prescriptions you will write for biologics next year?

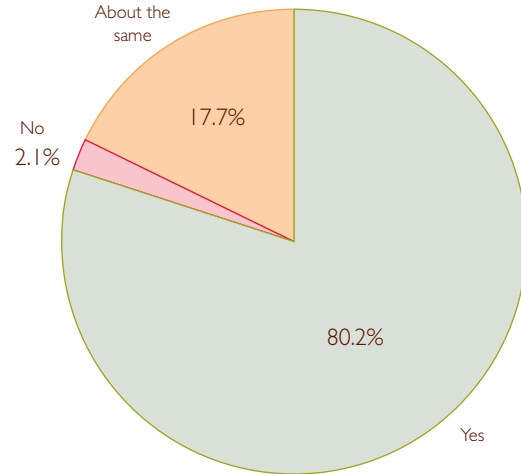


Figure 4: On average, what percentage of your time do you personally spend on the following responsibilities?

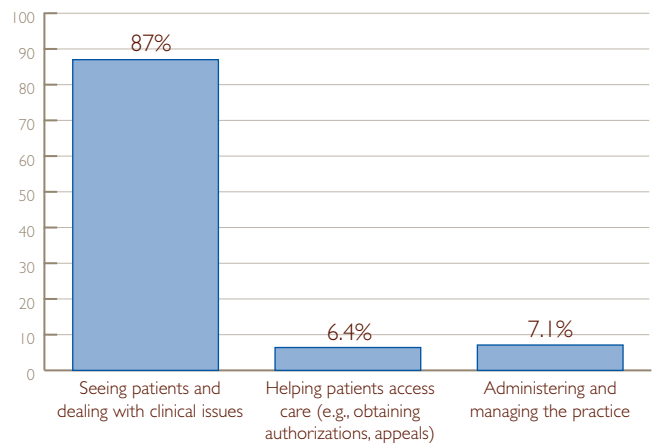
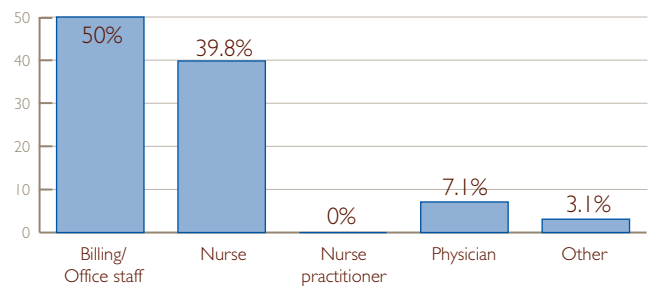


Figure 5: Who on your staff has the primary responsibility for obtaining prior authorizations and approvals from insurers?



Most rheumatologists devote a portion of their practice to treating conditions that are more common than serious inflammatory disorders, such as osteoarthritis or

fibromyalgia. Yet many respondents, including Diana Titova, a rheumatologist who practices in Lakewood, Washington, said they prefer to develop a treatment plan for patients with these more common conditions and send them back to their primary care physician to manage their treatment. “I try to keep patients whom only a rheumatologist can treat,” she said.

Weiss, too, said he prefers to focus on serious inflammatory disorders. “Primary care physicians have a low comfort level in treating these disorders,” he said, “and patients who have these conditions want and need the expertise of a rheumatologist. Patients want a specialist to treat them.”

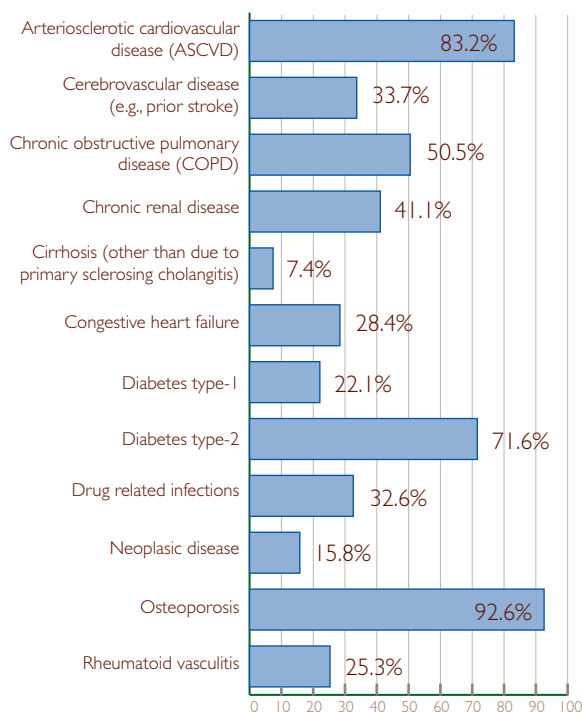
RA is a serious disease not only because of the damage it can cause to the joints, but also because it can be accompanied by or precipitate other diseases. Figure 6 shows a breakdown of diseases that respondents said are prevalent in their patients with RA. The most common are osteoporosis (93%), arteriosclerotic cardiovascular disease (83%), and type-2 diabetes (72%).

Two studies out of this year’s Annual Congress of the European League Against Rheumatism in Paris are part of the research that bears out an association between RA and these other, more common diseases. These two studies show that RA is an independent risk factor for cardiovascular disease.^{4,5} Another study, out of the Centers for Disease Control and Prevention earlier this year, shows that more than half of adults with diagnosed diabetes also have arthritis, and both the inflammatory process of RA and the corticosteroid drugs often used to treat it have been shown to lead to the brittle-bone disease osteoporosis.⁶

All of the survey respondents said they use biologic agents to treat RA, psoriatic arthritis, or ankylosing spondylitis. “If the percentage were any lower, I would say someone answering the survey shouldn’t be practicing rheumatology,” said Weiss.

“Everybody is writing the same number of prescriptions or more. Nobody has backed up,” said William Harrell, MD, a rheumatologist in private practice in Durham, North Carolina, who also holds a consulting faculty position at Duke University. “I think that is the tendency because there are new drugs coming out, and we are going to be using more, and we are going to become more comfortable with the older drugs.

Figure 6: Which of the following co-morbidities are prevalent in your patients with RA?



I think what people are saying is that use is stable and rising, and that it is going to continue to rise,” said Harrell.

But with the rise of the new technology comes a cost. Of those respondents (20%) who do not anticipate writing more prescriptions for biologics over the next year, more than two-thirds (67%) cited “too expensive for patients” as the reason.

Nevertheless, when asked how interested they are in trying a new biologic agent, the majority of physicians (56%) said they are very interested (Figure 7). Of several drugs currently in the pipeline, most respondents (78%) cited Actemra as the one they think will prove most valuable. Harrell said the most likely explanation is that Actemra will be the next biologic agent to hit the market. “They’re already getting a little bit of the hype going, and that’s why it’s getting good ratings. Actemra will be a once-a-month IV infusion,” he said.

Waxman suggests that Actemra’s pre-approval popularity is related to the fact that it is given by infusion. “Doctors who have infusion centers in their clinics can earn money in their office doing an

“Physicians are recognizing that patients do so well on [biologic] drugs that they are willing to put up with the hassles and go ahead with the treatment.”
—Jack Waxman, MD, Santa Rosa, California

Figure 7: Please check one box for each question below.

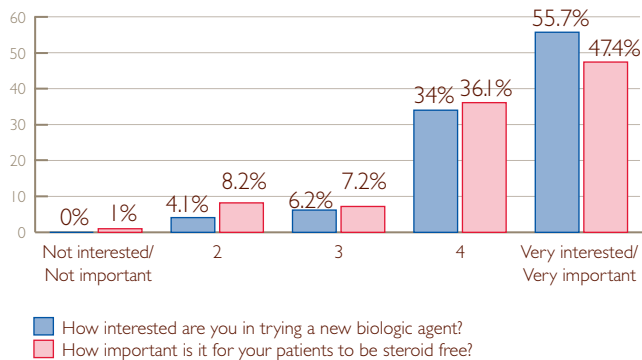
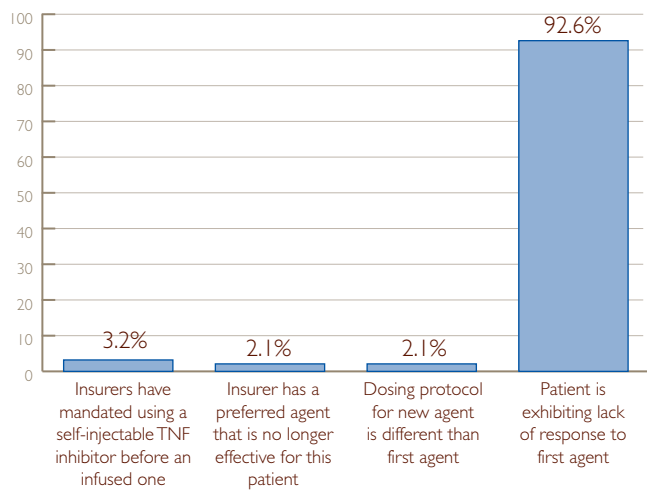


Figure 8: If your patients have switched between anti-TNF agents is it usually because:



infusion,” he said. “With some of [the agents], they can’t earn money because they are given by subcutaneous injection.”

Figures 9 through 11 denote the patient populations for which respondents would prescribe biologic therapy. The majority of respondents said they would prescribe biologic therapy for patients who had failed non-biologic therapy — 95% would do so for patients with RA or psoriatic arthritis, and 84% would do so for patients with ankylosing spondylitis. There was more variation in regard to respondents’ prescribing of these agents with newly diagnosed moderate disease: 56% for RA, 62% for psoriatic arthritis, and 74% for ankylosing spondylitis. For newly diagnosed mild disease, the willingness to prescribe biologic agents declined: 4% for RA, 3% for psoriatic arthritis, and 17% for ankylosing spondylitis.

Figure 9: Which patients with RA should receive biologic therapy?

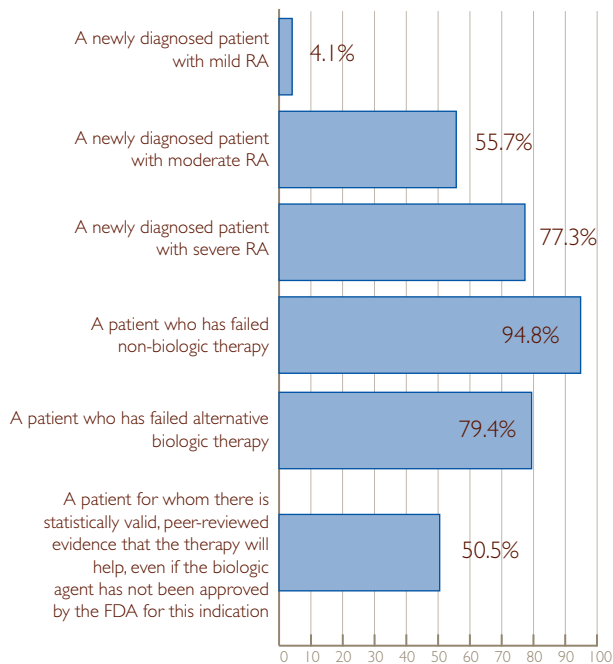
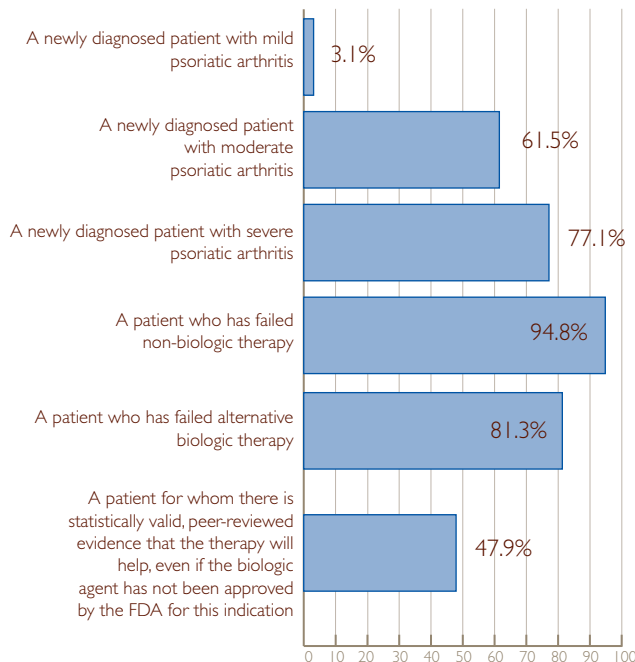
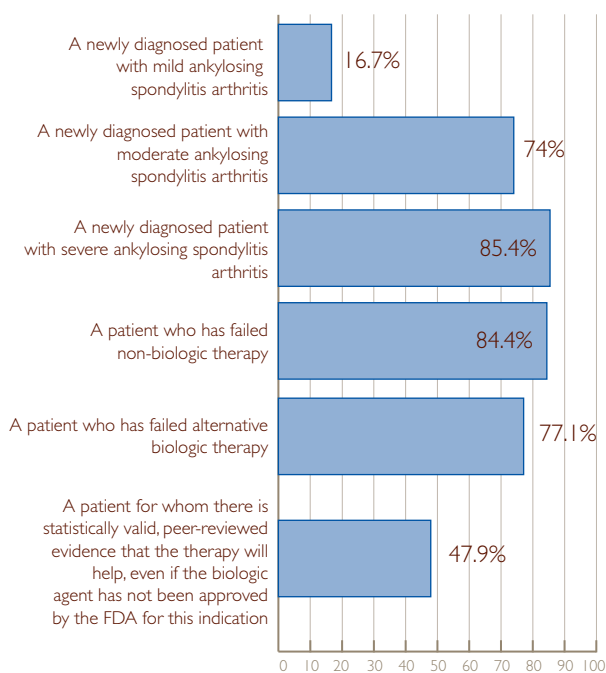


Figure 10: Which patients with psoriatic arthritis should receive biologic therapy?



Rheumatologists tend to prescribe biologic agents earlier for psoriatic arthritis and ankylosing spondylitis because there are fewer effective non-biologic agents for them, said Titova. Methotrexate, a disease-modifying drug, is often

Figure 11: Which patients with ankylosing spondylitis should receive biologic therapy?



effective for RA, but it does not work as well for spondy-larthropathies such as ankylosing spondylitis, Titova noted. People with psoriatic arthritis may be more susceptible to liver toxicity from methotrexate, she said.

Overall, said Weiss, the percentages of patients receiving biologic therapy should be “very high right now, because we know that [these agents] can reverse and prevent a lot of damage and morbidity and mortality. I am thinking doctors should at least be discussing [biologic therapy] with 65% to 70% of patients on their first visit.”

Three of the approved biologic agents — abatacept (Orencia®), infliximab (Remicade®), and rituximab (Rituxan®) — are given by infusion. When asked how their practice handles infusions (respondents could check all answers that applied), 81% said their clinic has facilities to handle infusions (Figure 12). Some respondents partner with a hospital outpatient infusion center (13%); some refer patients to an infusion center (8%) or to another practice that has an infusion center (6%).

“I think a year or two ago many fewer doctors had their own infusion clinics,” said Weiss. He attributes the increase largely to Medicare cuts and decreases

Figure 12: How does your practice handle infused medications?

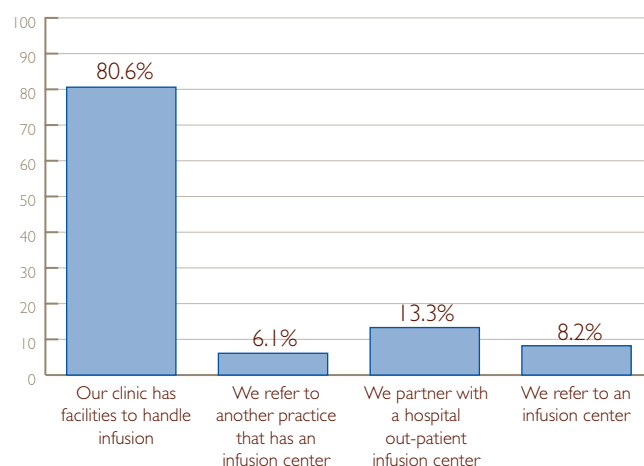
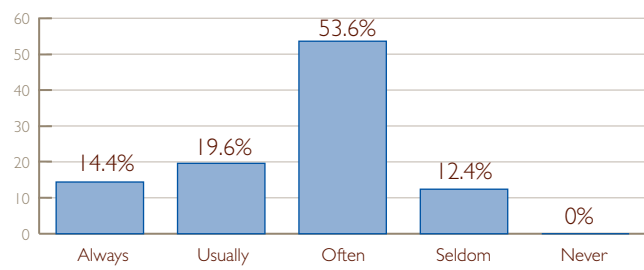


Figure 13: How frequently do insurers try to restrict the use of biologics?



in reimbursement that have left physicians in general looking for ways to improve their revenue. Physicians with their own infusion facilities can bill for the procedure.

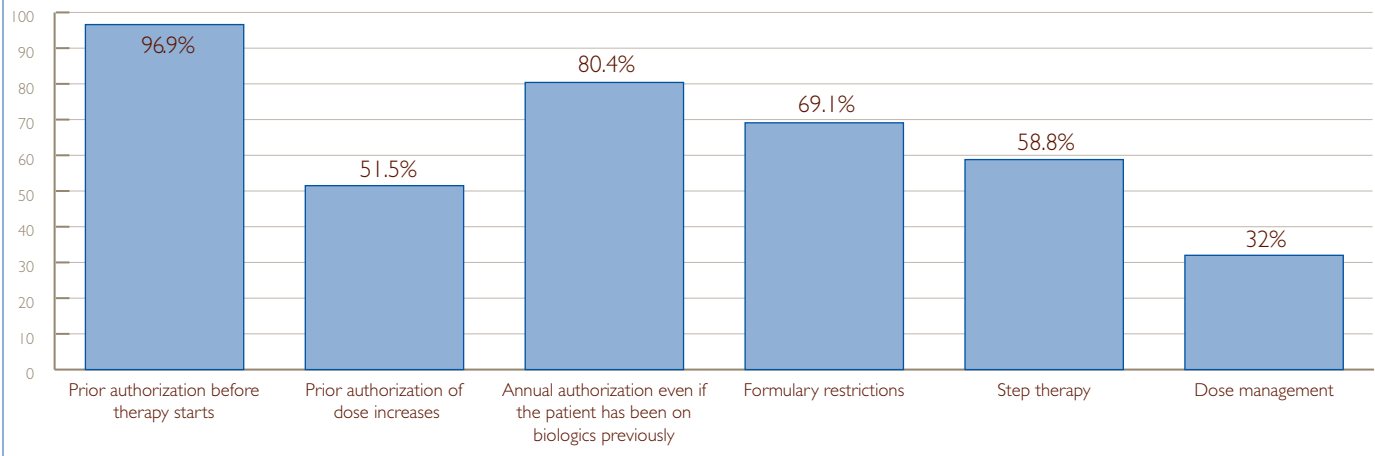
Respondents are in agreement that the availability of infusion services in the physician’s office benefits patients as well. “We can provide a service to the patient in a monitored care setting,” said Weiss. “We are able to infuse their biologic agents and give much better care to patients, as opposed to sending them out to local hospitals that

may or may not know much about that particular drug. So we give the patients better care,” he added.

“I think that without having infusion services it is really hard to stay mainstream,” said Harrell. “Providing infusion services in your office is superior to sending your patients to a hospital or infusion clinic. In your own office, you have control over what is going on with your patients. You can be on top of safety issues and make sure you

“Ninety percent of surveyed rheumatologists said they are interested in trying new biologic agents.”

Figure 14: What restrictions do insurers impose to limit the use of biologics?



have nurses who have appropriate experience with these drugs.”

Almost all respondents acknowledged that restrictions on biologics are a problem: 54% said that insurers often try to restrict the use of biologics; 20% said they usually do; and 14% said they always do (Figure 13). The most commonly cited restriction imposed by insurers was prior authorization before therapy starts, followed by annual authorization even if the patient has been on biologics previously (Figure 14).

“Prior authorization — that’s where hell starts,” said Weiss. Though doctors and their staff members may be required to make phone calls, write letters, and provide documentation on the patient’s disease and other medications he or she has taken, such efforts do not necessarily ensure approval.

“[Insurers] have a lot of different ways of keeping us from prescribing biologics,” said Weiss. “It’s a game. They have a lot of ways they go about doing that.”

Waiting for authorization of a request can be frustrating as well. While 40% of respondents said they receive an answer from insurance companies about a prior authorization request in two to four days, others said they generally wait between about a week (33%) and more than a month (1%) (Figure 15). While prolonging the time to approval may save the insurer money, at least in the short run, it can be detrimental to patients for whom receiving a biologic agent early can make a difference in the ultimate course of the disease.

“The key here is [the insurers] are not doing what is in the interest of the patient,” said Weiss. “They are doing it to save money. I have one patient right now who can’t get her medication, and she has been off it four to six weeks now.”

Figure 15: How much time does it generally take to receive an answer from insurers on a prior authorization request?

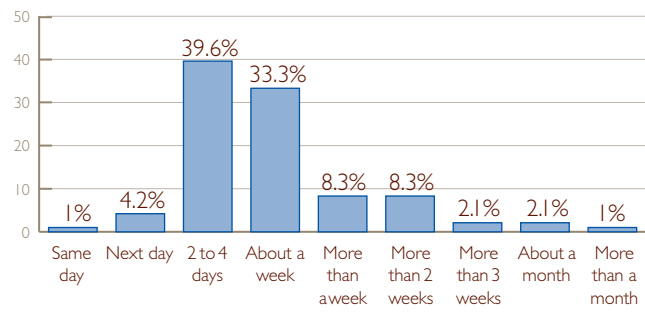
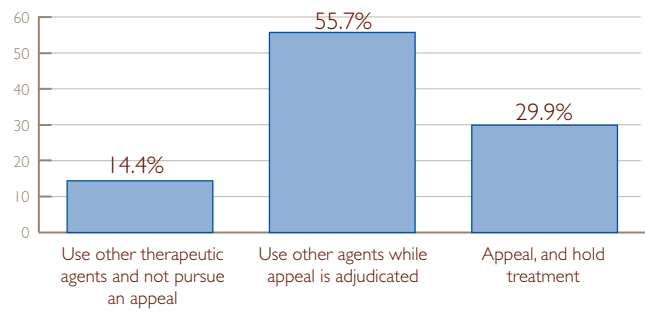
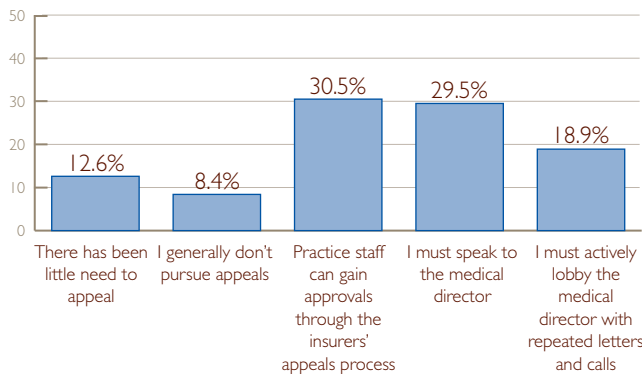


Figure 16: If your request for biologic therapy is denied, which of the following actions do you generally take?



When a request for biologic therapy is denied, most of the respondents pursue an appeal (Figure 16). Thirty percent of respondents said their office staff can gain approvals through the insurers’ appeal process, but much of the work involved in appeals is often borne by the physician. Almost 30% of respondents said that when working on an appeal they must speak to the health plan’s medical director; and 19% said they must actively lobby the medical director with repeated letters and calls (Figure 17).

Figure 17: How involved are you in the appeals process?



For many patients, insurance authorization alone does not ensure access to biologic agents. High co-payments often make biologic therapy unaffordable. To help put treatments within reach, manufacturers offer patient assistance programs. Ninety-eight percent of respondents said the Humira® program, called Humira Share, offers assistance to their patients; 92% said their patients use the Enbrel® program, called Quick Start; and 61% said their patients use the Remicade program, called Remi-Start. "Just about every one of these programs has done an excellent job," said Weiss.



Authorizing Biologics for RA Patients Already Taking Them

**The Comments of David I. Weiss, MD
Arthritis Associates
Hattiesburg, Mississippi**

David I. Weiss has been practicing internal medicine, pulmonary medicine, and rheumatology for two decades. He finds it increasingly difficult to obtain approval for biologic therapy — not only for new patients, but also for patients who are benefiting from biologic therapy now and need approval from their insurance companies to continue their treatment.

It's not surprising to me at all that more and more time is being spent trying to get approval for medications. There are a lot of new medications coming — a lot of high-dollar biologics. It is also time for generics of other medications to come out, and insurers save a lot of money by not approving some of these high-cost treatments.

The key here is that the insurers are not doing what is in the interest of the patient — they are doing it to save money. They are doing it to save money now, as opposed to prevention. For example, even if a medication could have a huge impact on preventing future problems or hospitalizations, that's really not what they're looking at. They are looking at saving that dollar that day.

It's not only hard to get a new biologic approved for a patient. Sometimes we have problems getting approval to continue a biologic a patient is already taking. That is happening now with one of my patients. She had been waiting on Humira, and her insurance would never approve it and kept denying it. My patient kept getting upset because she had been on it, and she needed to be approved to continue it.

Finally they sent a letter that said she needed to meet seven criteria — criteria that are used in RA drug studies, not clinical practice. So that's more unnecessary paperwork for me and more waiting for my patient who needs her medicine.

I deal with things like this all the time, and I find the problem is increasing. It used to be two to three or four weeks to get approval. Now I am finding it takes one or two months — easy. What I think they really want is to make it so difficult that you say to heck with them and try something else.

My patient can't get her medicine, and she has been off it four to six weeks now. I am running out of time. My patient is running out of time, too.

- ¹ Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Rheumatoid arthritis. Available at: <http://www.cdc.gov/arthritis/arthritis/rheumatoid.htm>. Accessed July 29, 2008.
- ² Cohen S. Biologic therapies in the treatment of rheumatoid arthritis. In *US Musculoskeletal Review 2006–June 2006*. Available at: <http://www.touchbriefings.com/cdps/cditem.cfm?NID=1857>. Accessed July 27, 2008.
- ³ Arthritis Foundation. Types of drugs. In *Arthritis Today*. Available at: http://www.arthritis.org/types-of-drugs.php?dt_id=3. Accessed July 29, 2008.
- ⁴ Van Halm VP, Peters MJL, Voskuyl AE, et al. Rheumatoid arthritis resembles type 2 diabetes as risk factor for cardiovascular disease: a cross-sectional study. *Annals of the Rheumatic Diseases* 2008;67 (Suppl 2):93.
- ⁵ Peters MJL, Van Halm VP, Voskuyl AE, et al. Prospective study reveals rheumatoid arthritis to be an important independent risk factor for incident cardiovascular disease. *Annals of the Rheumatic Diseases* 2008;67(Suppl 2):309.
- ⁶ Centers for Disease Control and Prevention. Arthritis as a potential barrier to physical activity among adults with diabetes — United States, 2005 and 2007. *Morbidity and Mortality Weekly Report*. 2008 (May 9);57(18):486-489.

Coding and Reimbursement



Plan providers have made many operational improvements over the past few years. The broad availability of electronic filing and access to contract information over the Internet have reduced the percentage of “lost” claims and have reduced the amount of time that office staffers need to follow up on information or hunt for it.

Today the onus is on individual practices to better understand the economics of their patient and provider relationships. As part of this task, practices need to take steps to increase profitability while maintaining appropriate levels of patient service. The present section of the *Biologics Trend Report* highlights a number of issues that require particular focus as part of this exercise.

More than 60 respondents with responsibility for managed care coding, billing, and reimbursement completed the coding and reimbursement portion of the survey. Ninety-eight percent of the respondents indicated that they work in gastroenterology and rheumatology practices; they are divided evenly in number between these specialties. Forty-three percent said they work in solo practices; 22% in single-specialty or multi-specialty clinics; and 19% in group practices. The average tenure at the current practice is 6.9 years, with an average of 9.6 years' experience.

Almost half of the respondents reported that their practice has a billing and reimbursement coder (Figure 1). The average number of full-time equivalents responsible for billing is 2.3. Almost a quarter of the surveyed practices use an outside billing service.

Individuals who were interviewed in regard to the survey results chose to comment on the reported 20 days that a new patient waits before coming in for an initial visit. They felt that practices are not only missing an opportunity to deliver a service that is typically profitable, but that they also risk losing a potential new patient and alienating the referring physician. The interviewees, even after allowing for some variation in geographic areas where specialists

are in short supply, felt that too many practices are missing an important opportunity by not seeing new patients within 48 to 72 hours.

Survey responses showed that even established patients wait an average of nine days for an appointment, though all interviewees acknowledged that patients with serious symptoms are seen immediately.

Respondents average almost 14 contracted plans per practice, and 36% reported Blue Cross Blue Shield as their “best” plan, based on timeliness and adequacy of payment, percentage of initial claims paid, and service provided in resolving billing and claims issues (Figure 2).

No interviewees expressed surprise that respondents ranked Medicaid the worst in these performance categories, though they noted that regional variations may occur (Figure 3). However, most felt that the high “worst” scores

for Blue Cross Blue Shield primarily reflect its size.

Interviewees said they would not have anticipated that more than 30% of respondents said their managed care plans are unprofitable, and that almost 16% did not know whether their managed care plans are profitable. Interviewees suggested that the lack of knowledge of, or

“**More than 30% of surveyed billing specialists said their managed care plans are unprofitable, and almost 16% did not know whether their managed care plans are profitable.**”

Figure 1: Who is primarily responsible for billing and reimbursement in your practice?

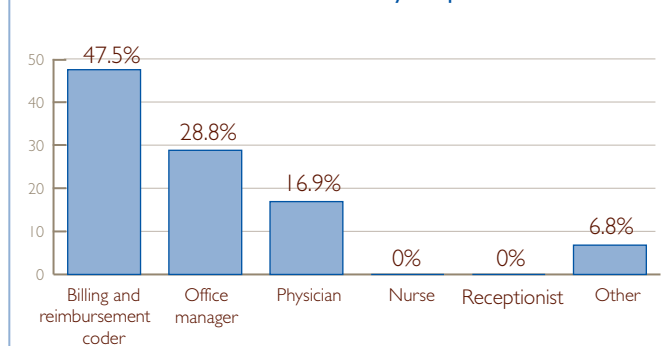


Figure 2: Please list your three best health insurance plans in terms of:

- timeliness of payment
- adequacy of payment
- percentage of claims paid cleanly on first pass
- customer service in resolving billing/claims issues

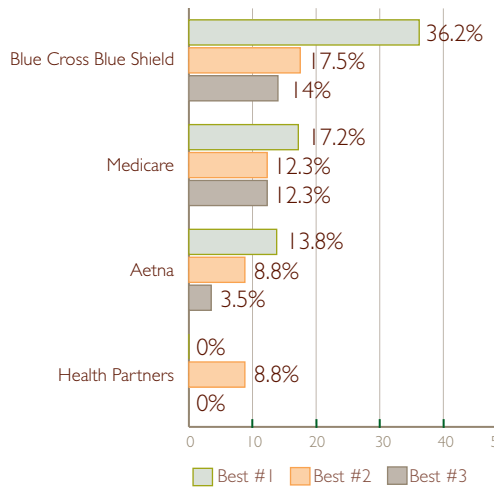


Figure 3: Please list your three worst health insurance plans in terms of:

- timeliness of payment
- adequacy of payment
- percentage of claims paid cleanly on first pass
- customer service in resolving billing/claims issues

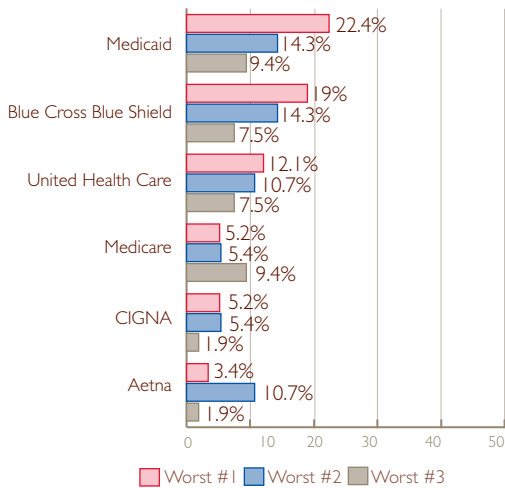


Figure 4: Which of the following is most accurate?

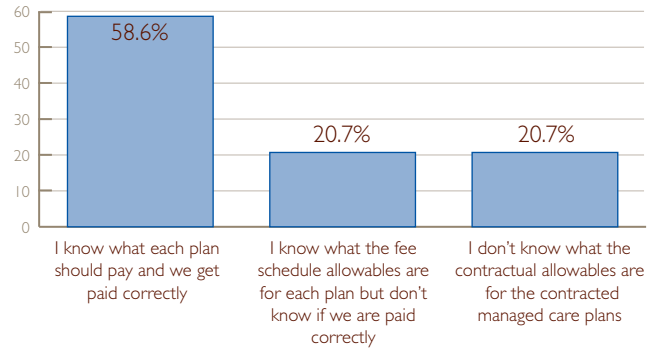
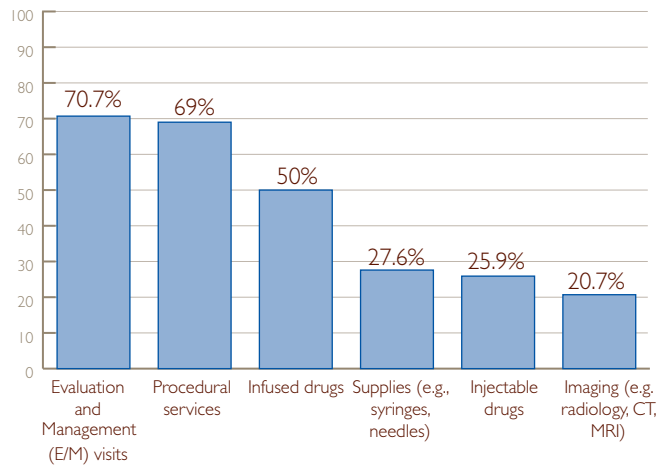


Figure 5: For which services do you feel the payment allowables should be increased?



interest in, this key contributor to the survival of a practice indicates, at best, that the billing staff has been isolated from the impact of their activities on the success of the practice, or, at worst, that the business side of the practice is conducted with a naiveté that may prove fatal. They pointed to a lack of understanding of compensation as the

core of the problem: only 59% of respondents reported a solid understanding of their plan's fee schedules and payment accuracy (Figure 4). That leaves more than 40% without a clear idea of how the practice will meet its financial obligations.

Almost 88% of respondents felt that most of their commercial managed care contracts pay either the same as or more than the Medicare fee schedule, but most also felt that the fee allowables for procedural services and evaluation and management (E&M) visits should be increased (Figure 5). More than one-third of respondents said they do not attempt to negotiate their fee schedule with their carriers.

More than 65% reported at least occasional success in negotiating fees with their carriers. A successful fee negotiation is a function of many variables, including the number of competing practices in the area, but is clearly an opportunity for those with the resources to pursue it.

One practice with the leverage to negotiate successfully is Gastroenterology Associates in Hilo, Hawaii. Its president, Edwin M. Montell, MD, said, "We're the only endoscopy center within 75 miles, so plans have to negotiate with us in order to ensure that this service is available to their subscribers."

Virtually all managed care plans (97%) now accept electronic claims, and most plans are perceived by respondents as paying in a timely manner; in 60 days or less. George S. Conomikes, president and CEO of Conomikes Associates in San Diego, estimated that probably close to 100% of correctly coded valid claims are paid within 30 days. He added that payment delays generally reflect errors in coding or other procedural issues that can be addressed with better training and management of billing staff. Two-thirds of respondents felt that claims filing limits are reasonable, but Conomikes notes that "claims should be processed long before the typical 180-day limit approaches. Any practice that has this kind of billing delay has an opportunity to significantly improve its financial position with better management of this process."

Respondents' experience with disputed claims and payments indicates another opportunity to improve the practice's financial position. More than half of the respondents indicated a lack of consistent success in this area (Figure 6). Interviewees suggested that, again, this problem is connected to accurate coding of the original

Use of provider manuals and websites by billing specialists may reduce long wait times on the phone for a possibly inaccurate response from a provider representative.

claim, along with timely submission and an understanding of the plan's coverage, including appeals options with which many respondents seemed to be unacquainted.

Interviewees also stressed that resources spent on training and managing billing staff can offer a satisfactory return for practices that are losing income owing to the delay or denial of claims, not only by increasing the percentage of first-pass bill approvals, but also by increasing employee job satisfaction and reducing turnover. Lorraine Schmidt, office manager at Arizona Gastroenterology in Phoenix, observed that "billing staff members

need to be persistent and creative. Valid claims will almost always be paid."

Almost 44% of respondents identified the plan's website as the best way to access key information about the plan, and 26% favor contacting a provider representative. Twenty-one percent said there is no easy way to access information. Only 9% said that reading carrier bulletins and the provider's manual is the best way to access information. Interviewees were less positive than were survey respondents on the value of contacting a provider representative in most situations. Most respondents said wait times of more than 15 minutes are common (Figure 7), and almost 30% said that information from provider representatives is frequently incorrect. Training for billing staffers that includes familiarizing them with provider

Figure 6: What is the usual outcome when you appeal an incorrectly paid claim?

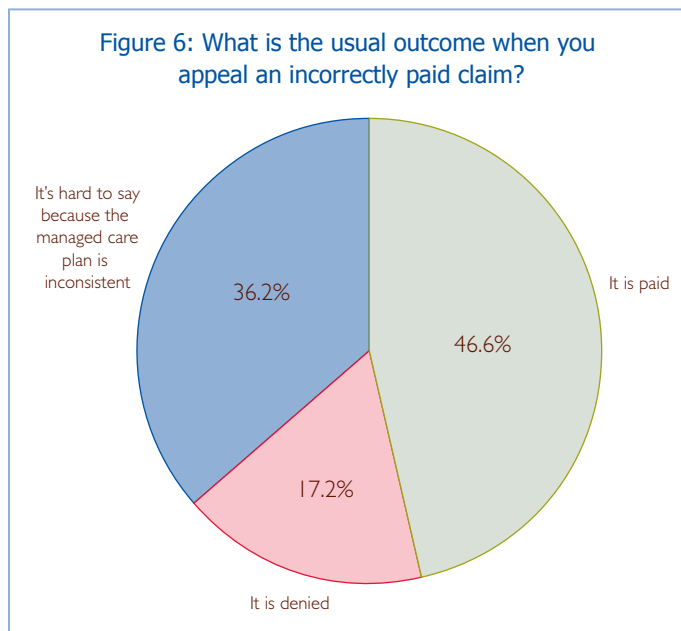
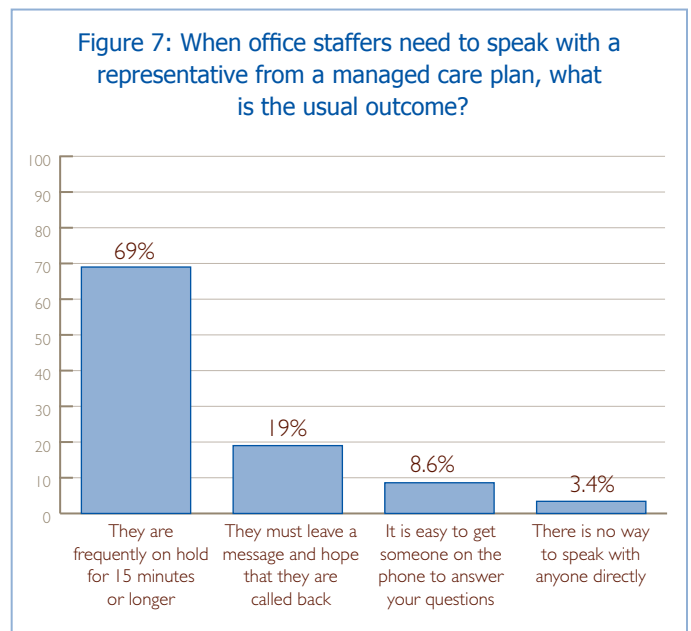


Figure 7: When office staffers need to speak with a representative from a managed care plan, what is the usual outcome?

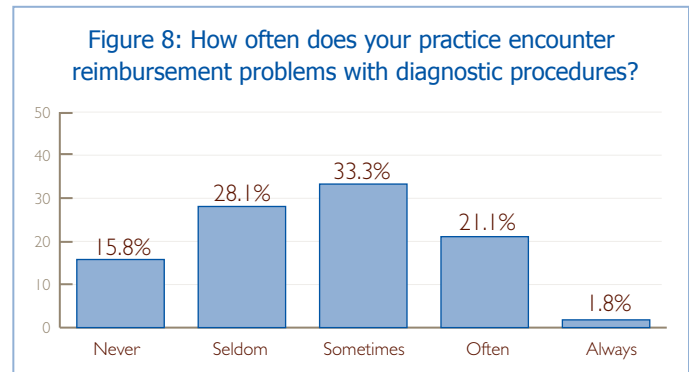


manuals and websites can reduce time spent waiting on the phone for a possibly inaccurate response from a provider representative, said interviewees.

Respondents were asked to identify from a list of ICD9 codes related to CD the ones that most frequently require an appeal or review for proper payment. Gastroenterologists rated 555.9-Unspecified site as the one most likely to require an appeal or review. Respondents were also asked to identify from a list of ICD9 codes related to ulcerative colitis the ones that most frequently require an appeal or review for proper payment. Gastroenterologists rated 556.6 Universal (pan colitis) as the one most likely to require an appeal or review.

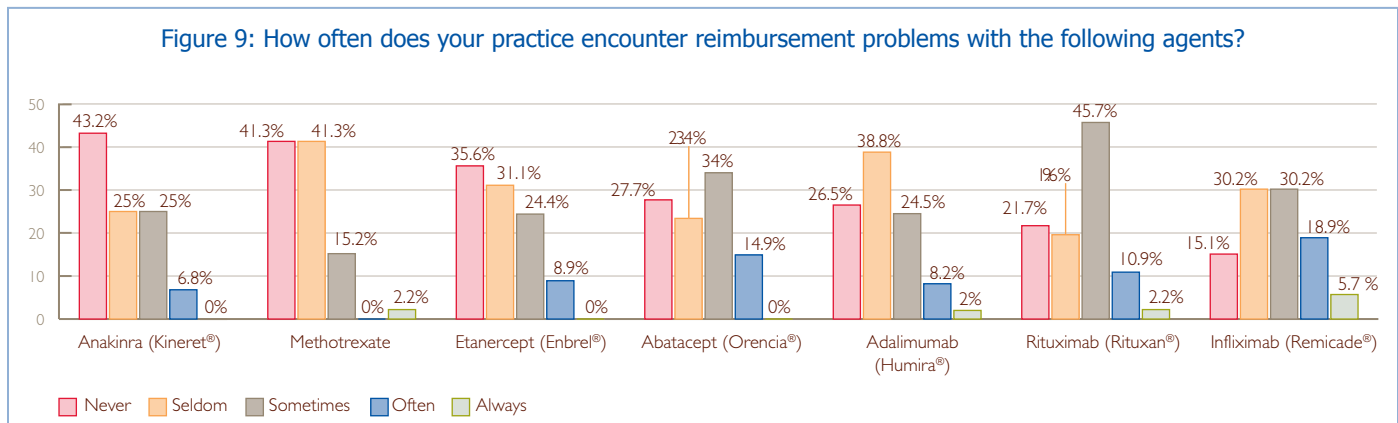
Respondents were asked to identify from a list of modifiers the ones most frequently ignored by third-party payers. Modifier -51, multiple procedures, and modifier -25, E/M service by the same physician on the same day of the procedure or other service, were chosen most frequently by 25% and 23% of respondents, respectively.

Twenty-one percent of respondents said they often encounter reimbursement problems for diagnostic procedures, and 33% said they sometimes encounter these problems (Figure 8).



Respondents were asked to select the diagnostic procedures that are frequently associated with reimbursement problems. "Fluorescent antibody, screen and antibody (CPT 86255)" and fecal occult test were chosen most often, by 23% and 20% of respondents, respectively.

The agents that respondents most often associated with reimbursement problems were Remicade® (infliximab) and Rituxan® (rituximab) (Figure 9). Robert D. Herman, MD, a partner at Goldstein Siegel Herman MD PC in Great Neck, New York, noted that his practice protects itself by requiring pre-approval from the patient's plan before administering high-cost drugs. He further observed that "the first six months are when we see reimbursement problems. Once the claim processors are familiar with the new codes, things run a lot more smoothly."



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Patients treated with CIMZIA are at an 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. CIMZIA should be discontinued if a patient develops a serious infection or sepsis. Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before CIMZIA use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA 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. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with CIMZIA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Serious and sometimes fatal infection due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens has been reported in patients receiving TNF-blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most common. Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients with chronic or recurrent infection, who have been exposed to tuberculosis, 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.

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating CIMZIA and periodically during therapy. Patients should be closely monitored for the development of signs and symptoms of infections during and after treatment with CIMZIA, including development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. CIMZIA should be discontinued if a patient develops a serious infection or sepsis. Patients who develop a new infection during treatment with CIMZIA should be closely monitored and undergo a prompt and complete diagnostic workup appropriate for immunocompromised patients, and appropriate antimicrobial therapy should be initiated. Appropriate empiric antifungal therapy should also be considered while a diagnostic workup is performed for patients who develop a serious systemic illness and reside or travel in regions where mycoses are endemic.

Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. Some cases have been fatal. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating CIMZIA therapy. Exercise caution in prescribing CIMZIA for patients identified as carriers of HBV. Patients who are carriers of HBV and require treatment with CIMZIA should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, discontinue CIMZIA and initiate effective anti-viral therapy with appropriate supportive treatment.

During controlled and open-labeled portions of CIMZIA studies of Crohn's disease and other investigational uses, malignancies were observed at a rate (95% confidence interval) of 0.6 (0.4, 0.8) per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 (0.2, 1.7) per 100 patient-years among 1,319 placebo-treated patients. The size of the control group and limited duration of the controlled portions of the studies preclude the ability to draw firm conclusions. In studies of CIMZIA for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 CIMZIA-treated patients and one case of Hodgkin lymphoma among 1,319 placebo-treated patients. The potential role of TNF blocker therapy in the development of malignancies is not known.

Symptoms compatible with hypersensitivity reactions, including angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria, have been reported rarely following CIMZIA administration. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy.

Use of TNF blockers, including CIMZIA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA; the causal relationship to CIMZIA remains unclear. Exercise caution in considering the use of CIMZIA in patients with these disorders.

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) has been infrequently reported with CIMZIA. The causal relationship of these events to CIMZIA 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 CIMZIA. Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, etanercept, with no added benefit compared to etanercept alone. Therefore, the combination of CIMZIA and anakinra is not recommended.

Interference with certain coagulation assays has been detected in patients treated with CIMZIA. There is no evidence that CIMZIA therapy has an effect on *in vivo* coagulation.

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. CIMZIA has not been formally studied in patients with CHF. Exercise caution when using CIMZIA in patients who have heart failure and monitor them carefully.

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

Do not administer live vaccines or attenuated vaccines concurrently with CIMZIA.

In controlled Crohn's clinical trials, the most common adverse events that occurred in $\geq 5\%$ of CIMZIA patients ($n=620$) and more frequently than with placebo ($n=614$) were upper respiratory infection (20% CIMZIA, 13% placebo), urinary tract infection (7% CIMZIA, 6% placebo), and arthralgia (6% CIMZIA, 4% placebo). The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for CIMZIA and 7% for placebo.

CIMZIA should be administered by a healthcare professional.

Suggested uses for this report:

- Presentations
- Comparisons
- Benchmarking
- Formulation of Policies
- Business Plans
- Budgeting
- Strategic Forecasting
- Analysis and Trends

