PERSPECTIVE

Kaiser Permanente's Evaluation And Management Of Biotech Drugs: Assessing, Measuring, And Affecting Use

A large integrated delivery system reports on its management of specialty pharmaceuticals.

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ABSTRACT: Two decades into the age of high-cost biotechnology medications, health care organizations are challenged to provide safe, effective treatment while managing costs. In a market lacking generic biotech drugs, health care organizations have few opportunities to negotiate reduced pricing; other strategies must be devised to manage use. Kaiser Permanente leverages its integrated health care delivery system to deploy management tools for costly therapies: evidence analysis, usage measurements, and multidisciplinary planning. Evidence-based medicine and realization of value provided by new therapies will depend on data capture and outcomes measurement, tools that are crucial to Kaiser Permanente's management of biotechnologies and effective use of members' financial resources. [*Health Affairs* 25, no. 5 (2006): 1340–1346; 10.1377/hlthaff.25.5.1340]

BIOTECHNOLOGY DRUG introductions have expanded treatment options for many diseases during the past twenty years, a trend expected to continue. Treatment costs have also increased dramatically, because new biotech drugs carry high price tags. The difference in the current annual cost of drug treatment from a decade ago can amount to tens or even hundreds of thousands of dollars per patient per year for certain target diseases (Exhibit 1).[1] Such costs exceed most patients' ability to pay for the drugs, especially during prolonged therapy. Therefore, the market for these drugs exists primarily where insurers or health care organizations are able to spread the high costs across a large group of insured people.

At Kaiser Permanente (KP) in California, biotech products have greatly increased drug costs, particularly in oncology, rheumatology, neurology, endocrinology, and dermatology. Some conditions, formerly untreatable, might now have a single, very costly treatment available. For example, KP California spends more than $10 million annually for biotech-derived enzyme replacements to treat approximately

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EXHIBIT 1
Drug Treatment Costs At Kaiser Permanente, Selected Years 1990–2005

Condition treated	Selected biotech drugs (with FDA approval year)	Approximate treatment costs per patient per year for drugs only (average or common low-and-high) 1990	1995	2000	2005
Multiple sclerosis	Betaseron (1994); Avonex (1996); Copaxone (1997); Rebif (2002)	–[a]	$13,000	$11,000–$13,000	$15,700–$21,000
Rheumatoid arthritis	Enbrel (1998); Remicade (1999); Kineret (2001); Humira (2002)	$1,100	$1,400–$3,500	<$1,400 with nonbiologics; ~$15,000 or more with biologics[b]	<$1,500 with nonbiologics; ~$18,000 or more with biologics[b]
Psoriasis	Enbrel (2004); Amevive (2003); Raptiva (2003)	$1,100	$1,400–$6,000	$1,400–$7,800	Up to $22,000 if biologics used
Crohn's disease	Remicade (1998)	$150–$900	$200–$8,000	Up to $9,500 or more with Remicade[b]	$16,500 or more with Remicade[b]
Hepatitis C	Intron (1983); Roferon (1984); Rebetron (1998); Peg-Intron (2001); Pegasys (2002)	–[a]	$2,300	$5,700–$17,000	$7,700–$21,000
Gaucher disease	Ceredase (1991); Cerezyme (1994)	–[a]	$115,000–$405,000	$125,000–$430,000	$125,000–$430,000
Fabry disease	Fabrazyme (2003)	–[a]	–[a]	–[a]	$180,000–$320,000
Cancer indication	**Selected biotech drugs**	**Approximate costs for treatment periods or cycles for drugs only (average or common low-and-high)[c]**			
Non-Hodgkins lymphoma	Rituxan (added in 1997)[d]	$600 per 8 weeks	$1,800 per 8 weeks	$26,600 per 8 weeks	$32,500 per 8 weeks
Breast cancer (recurrent or metastatic)	Herceptin (added in 1998)[e]	$1,150 per 6 months	$1,400 per 6 months	Up to $32,000 per 6 months with Herceptin	Up to $36,000 per 6 months with Herceptin
Metastatic colorectal carcinoma	Avastin (2004); Erbitux (2004)	$750 per 8 weeks	$900 per 8 weeks	~$1,000–$7,750 per 8 weeks	Up to ~$28,500 per 8 weeks with Avastin or Erbitux

SOURCE: Drug costs are based on average wholesale price (AWP) from the *Red Book* (Thomson Healthcare Inc., 1990, 1995, 2000, and 2005). Although most organizations can achieve contracted prices at some discount from AWP, discounts for biotech drugs are usually not large: 5–10 percent in some cases and slightly more or less in other cases.

NOTES: All costs are approximations based on common treatment regimens available in the index years. For doses based on body weight, a range of 50–90 kg or an average of 70 kg was assumed. For doses based on body surface area, an average of 1.73 square meters was used. Year of Food and Drug Administration (FDA) approval is in parentheses.

[a] Supportive treatment only.

[b] Remicade costs have been reported to be higher in some patients because of progressively increased dosing requirements.

[c] The number of cycles used over a given time period will vary widely. With adequate response and lack of disease progression or toxicity, multiple cycles may be administered. If disease progression occurs, a second- or third-line treatment regimen might be started (which could also increase treatment costs).

[d] Radio-labeled monoclonal antibodies are also available but are not included here.

[e] Other biotech drugs are being studied, including Avastin.

fifty patients with various rare, inherited enzyme deficiencies associated with severe health problems and early mortality. For these patients, there are no lower-price alternatives.

Some of the newer biotech products have yet to reach their full market potential. In early 2006, IMS reported that only 10 percent of patients diagnosed with rheumatoid arthritis (RA) are treated with the latest drugs (such as Remicade, Enbrel, and Humira).[2]

Growing use translates to higher costs per member for administration of pharmacy benefits across the plan. For biotech-derived drugs plus a few other specialty biologics (for example, immune globulins, alpha-1 antitrypsin, and clotting factors), total KP California spending has tripled in the past five years and more than sextupled in the past eight years.[3] With increases likely to continue, high-price products must be tracked closely, so that their use can be factored into drug use management strategies. At KP, where approximately 95 percent of members have a drug benefit, managing the overall impact of new costly therapies is critical.

In this effort, KP relies on its structure as an integrated delivery system (IDS), which encompasses Kaiser Foundation Health Plan Inc., Kaiser Foundation Hospitals, and the Permanente Medical Groups. Physicians oversee clinical care, and the organization promotes coordination between the health plan (including the pharmacy organization) and the medical groups. KP's organization permits coordinated management of biotech drug use through multidisciplinary assessment of available evidence, usage and outcomes measurement, and therapy initiatives to optimize both clinical outcomes and resource use.

These strategies are especially important for managing biologics because there is little competition among them and therefore little or no opportunity to negotiate lower prices, except within a few classes of drugs (human growth hormones, erythropoietin analogs, and insulin). As a direct purchaser with close cooperation between the medical group and the organization delivering the drug benefit, KP can generally secure large price advantages where it can shift market share among a therapeutic class of competing agents. Most KP cost-control efforts are focused on identifying the potential health value offered by these drugs and directing them to the patients who stand to benefit from them.

Assessing The Evidence

Committees of Permanente Medical Group physicians make formulary decisions and adopt guideline recommendations. As an integral part of the process, pharmacists from KP Drug Information Services evaluate relevant clinical trial evidence with physician-experts.[4] With this support and advice, individual KP California physicians make prescribing decisions for their individual patients.

For biotech drugs, the effort is coordinated through a formal, centralized multidisciplinary group—the Biotechnology and Emerging Pharmaceutical Technology Assessment Committee (BEPTAC)—prior to review by KP's Northern and Southern California Pharmacy and Therapeutics (P&T) Committees.

There are special considerations related to biotech drugs. Because of the Food and Drug Administration's (FDA's) accelerated process for certain classes of drugs, some have been approved without published randomized clinical trial evidence. At KP, available evidence is systematically reviewed and weighed in a coordinated internal evaluation process.

For example, the FDA granted accelerated approval for Tysabri (natalizumab)—an intravenous infusion to treat multiple sclerosis (MS)—in 2004 based on data from two incomplete clinical trials.[5] KP pharmacists and neurologists reviewed the limited available evidence and drafted consensus guidelines recommending that patients whose condition was well controlled on other MS therapies should not be switched to Tysabri without further efficacy and safety data. In early 2005, evidence of serious adverse effects in the ongoing clinical trials emerged; cases of progressive multifocal leukoencephalopathy (PML), a rare and potentially fatal disease of the central nervous system, were confirmed. The drug's manufacturer suspended marketing in February

2005, and the FDA issued a public health advisory pending a thorough safety investigation.[6] Had KP conservative guidelines not been used, more patients could have been exposed to Tysabri prior to the discovery of PML.

KP's evidence assessment also addresses "off-label" prescribing of biologics. At KP California, individual physicians make point-of-care decisions based on published evidence, alternatives, and individual diagnoses. Information regarding off-label uses and supporting evidence is vital; KP Drug Information Services operates a consultive service to find published evidence at an individual physician's request. In some cases, KP's Drug Information Services conducts more formal evidence review for off-label indications and presents results to specialist physician committees. Experts might conclude that the evidence supports an off-label use in a subset of patients or under certain circumstances. The committee might recommend that other potential candidates be referred to a clinical trial.

Measuring Usage And Outcomes

With costly new biologics, KP takes advantage of its IDS and its investment in health information technology (IT) to monitor drug usage and communicate information about that usage to prescribers. KP can access large stores of internal data to generate statistics on drug use, even across separate databases. Purchase records and computerized pharmacy dispensing records provide detailed data on outpatient prescription use, while drugs administered in the hospital, clinic, or physician's office are captured in local usage records at each KP medical center. Data are comprehensive but not fully integrated.

Planned upgrades to KP HealthConnect, a computer-based organizationwide decision-support system, will integrate inpatient and outpatient clinical records for KP's 8.5 million members; centralized databases will improve programwide data access and permit better data review and analysis. KP HealthConnect will also provide other decision-support tools, such as online evidence-based protocols and best-practice alerts.

■ **Usage totals.** In the past five years at KP California, biotech drug spending has nearly tripled, while total KP health plan membership has grown 5.3 percent. The 2005 spending for biotech drugs reached 18 percent of total drug spending, up from 10 percent in 2000. The cost per member per month for biotech drugs rose 195 percent in the past five years and 505 percent in the past eight years, as a result of the increased use of biologics as well as the rising costs per patient.[7]

Tracking total spending by drug category reveals important usage trends. For example, KP California's spending for a group of biologic immunomodulatory drugs—used to treat RA, psoriatic arthritis, psoriasis, Crohn's disease, and other conditions—increased 305 percent from 2001 to 2005. More detailed analysis of this trend showed that costly new biologics, costing $12,000 or more per patient per year, were supplanting drugs that had cost a few hundred dollars per patient per year.

At the same time, drug manufacturers continue to raise prices for existing biotech drugs. Prices for MS drugs have increased rapidly since they emerged during the 1990s—some as much as 50 percent from 2000 to 2005. Over that same five years, the number of patient-years of MS drug treatment for KP California grew 101 percent. The resulting total MS drug spending rose 201 percent.

■ **Tracking individual usage.** The ability to measure details of usage at the individual patient level—to "drill down" to variables such as age group, benefit coverage, dosage patterns, prescriber patterns, and indication mix—is a powerful analytic tool. KP California's long-established outpatient pharmacy information system has allowed such detailed data tracking.

For outpatient drugs such as Enbrel, used to treat rheumatologic conditions or psoriasis, data are monitored by indication and provider specialty. Based on results, KP California rheumatologists and dermatologists develop or re-evaluate criteria that address the various indications. Upgrades to KP HealthConnect will improve tracking efforts for clinic-infused drugs used to treat similar conditions, such as

Orencia or Remicade.

KP HealthConnect will also permit closer observation of dosage requirements per patient, allow forecasting for expenses associated with variable dosing regimens (such as in oncology), and allow identification of "dosage creep" (a potential issue for some biotech protein–based drugs, possibly related to formation of antibodies against the drug protein).

Clinical Outcomes Measurement

At KP California, outcomes measurement for biologics has often depended on manual data gathering. For example, a recent KP California medication use evaluation (MUE) for Xigris (drotrecogin alfa) used medical chart abstraction by inpatient pharmacists. The data were used to examine criteria compliance, adverse effects, and efficacy outcomes for patients given Xigris for sepsis in intensive care units located at twenty-seven Kaiser hospitals. Preprinted orders with attached guidelines presented criteria to prescribers at the time they were ordering Xigris.

Results from the MUE were reviewed by critical care and infectious disease specialists. The physicians could compare their own hospital's experience with collective results, such as how closely prescribers followed certain criteria. Also, physicians could examine risk-related events (such as bleeding) and their correlation to risk factors for Xigris (such as recent surgery or trauma).

Xigris was approved in 2001 after the FDA Anti-Infective Drugs Advisory Committee split on whether to recommend approval, with several members recommending a confirmatory trial.[8] In the absence of that confirmatory trial, the MUE gave KP physicians important information and an outcome-oriented perspective on the use of the drug.

Affecting Use

Providers and insurers that are committed to prudent spending must optimize their use of resource-intensive therapies such as biologics and other drugs with high costs per patient—sometimes called "specialty pharmaceuticals." Some organizations follow processes such as prior authorization to certify treatment as a covered benefit; however, KP, with its unique organization, can use other techniques to promote the most appropriate use for this group of drugs.

■ **Alternatives to prior authorization.** Prior authorization, as used outside of KP, often involves centralized approval for drug therapy based on satisfaction of specific criteria. When the criteria are not met, coverage might not be immediately available for the requested therapy.

Within KP, individual physicians determine whether a given therapy will be used. Physicians prescribe based on various factors: clinical evaluation, available alternatives, available evidence, expert consensus, disease management plans, and their own experience.

KP uses several key methods to manage usage within this prescriber-driven model. These strategies include physician-developed guidelines, criteria-based prescribing, pharmacist-managed therapy, member education, specialty pharmacy programs, advisory panels comprising specialist physician advisers, and patient registries to conduct therapy surveillance. Key initiatives are described below.

KP has also identified important goals for future development, including outcome-informed prescribing, conversion to generic equivalents of biologics, and ongoing improvement and expansion of electronic medical records (EMRs) and decision-support systems.

■ **Key current and future initiatives.** *Guidelines.* In broad terms, biotech drug guidelines are intended to educate, advise, and model the safest, most effective, and most efficient use in various settings. Guidelines might also identify best candidates for therapy, define a step-therapy approach, provide important recommendations for safe dosing or monitoring, and offer risk-versus-benefit perspectives.

At KP, evidence-based guidelines are prominent tools for managing biotech drugs; they have been developed by physicians and pharmacists for drugs accounting for more than 60 percent of all biotech drug purchases. As an example, Xolair (omalizumab) guidelines include recommended criteria for usage, as well

as other information to help the prescriber manage therapy, such as exclusion criteria, dosage and administration guidance, and monitoring methods and forms. The original guidelines drew upon evidence from clinical trials presented to the FDA for approval.[9] Original Xolair guidelines were adopted in 2003, soon after the FDA approved the drug. In 2005 KP revised guidelines based upon newer literature, including identification of patient types most likely to benefit from the use of Xolair.[10] The Xolair guidelines will be reconsidered when further published data or internal monitoring indicate a need for revision.

Criteria-based prescribing. Measurement of criteria compliance has been evaluated for other biotech drugs. Results allow prescribers to evaluate prescribing practices, inform specialist physician committees about the effect of their guideline criteria, and begin reassessment of the criteria themselves.

Criteria compliance is now being measured for KP guidelines regarding use of disease-modifying anti-rheumatic drugs (DMARDs) to treat RA. An objective of this review is to demonstrate whether nonbiologic DMARDs (such as methotrexate) were appropriately used prior to starting one of the biologics (such as Enbrel, Humira, or Remicade). The metric designed for this review screens for duration of nonbiologic DMARD treatment before conversions to a biologic DMARD; it also screens for patient's age and other conditions (such as liver problems) that could affect the choice of drugs. This metric, still being refined, has already revealed important information about treatment patterns and identified opportunities to improve prescribing practices, refine guideline criteria, and demonstrate criteria adherence.

Pharmacist-managed therapy. During the past three decades, clinical pharmacists at KP California have become increasingly involved in managing therapy for individual patients, initially in the inpatient setting, then in ambulatory care, and most recently in the management of specialty pharmaceuticals. This involvement occurs in collaboration with, and under the oversight of, treating physicians.

More recently, KP has developed programs for pharmacist management of biotech drugs such as erythropoietins and colony-stimulating factors. Pharmacists consult with patients and work with physicians to apply guideline criteria for dosing, implementing dose adjustments and discontinuing treatment based on patient parameters, thereby assuring that patients receive the drug when needed and stop the drug once goals have been reached.

■ **Developing future methods.** *Outcome-informed prescribing.* Physicians already use individualized outcomes to adjust therapy for individual patients. Evaluation of carefully designed outcomes measurement for a large population, applied prospectively to guide drug use—outcome-informed prescribing—can help prescribers use biotech drugs more effectively. At KP, this method is evolving as an important future initiative, especially for biologics for which clinical trial data are limited or whose outcomes in clinical trials were narrowly defined.

Generic equivalents. For many small-molecule drugs, KP has successfully implemented organizationwide, value-based prescribing, including shifting to generic equivalents where appropriate. As a result, KP has a history of moving sizable market share from one product to an equivalent one, to reduce costs while maintaining quality of care. When biosimilar equivalents (also called biogenerics or follow-on protein products) for biotech drugs become available in the United States, KP expects to carefully evaluate these products and switch to biosimilar equivalents where appropriate. The use of equivalents will be guided by current processes for assessing, measuring, and managing drug use.

Concluding Thoughts

Biotech drugs present challenges to the delivery of high-quality, cost-effective, equitable health care, including impact on disease treatment, limitations of efficacy and safety data, opportunities for off-label indications (prior to the availability of clinical trial evidence), and high resource use. Future technologies, such as antisense drugs, cell therapies, cancer

vaccines, gene therapy, pharmacogenetics, and many new specialty pharmaceuticals, will pose both similar and new challenges to health care organizations.

KP, as a large purchaser, has traditionally been able to obtain discounts within a therapeutic class of competing agents. In the biotech sphere, populated by unique therapies and no generics, opportunities are limited. Thus, KP has sought to leverage its unique organization to devise other approaches to achieve reasonable drug usage management with respect to biologics and other costly therapies. This stands in contrast to the prior authorization approach more common in less integrated health organizations.

These strategies should be considered in a larger context. With the expansion of Medicare prescription drug coverage, federal policymakers are no longer mere arbiters of commercial conflict between the biotechnology and health insurance industries. Policy decisions relating to biotech drugs will carry significant federal budget implications in terms of the cost of Medicare drug coverage. Within the framework of these policy decisions, whether practices now being developed by IDSs can be more widely adopted will determine whether taxpayers will get their money's worth when it comes to biologics.

The question of future approval of follow-on biologics is critical. The availability of competing biologics could provide a stimulus to drug industry leaders to continue to innovate. As current pricing reflects, the balance of access and affordability, which has been struck reasonably well in the small-molecule drug market, has yet to emerge with biotech drugs. Whether the health insurance system can sustain financing of items and services for which there are no competitors—even with the application of effective management techniques—remains to be seen.

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NOTES

1. Many biotech drugs have had an important impact on the clinical course of difficult-to-treat conditions and have also raised the drug costs for treatment. Exhibit 1 summarizes the impact on the upper end of drug costs for some of those indications. The clinical effect of some newer therapies might either decrease other nondrug health care costs (through lesser morbidity or mortality, fewer medical office visits, and so on) or increase other health care costs (through increased visits to infusion centers, treatment of adverse effects, decreased complications allowing longer treatment, and so on). These cost impacts are more difficult to quantify.
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3. Authors' analysis based on KP data.
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