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Redirecting Innovation in U.S. Health Care: Options to Decrease Spending and Increase Value

Case Studies

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CASE STUDY 1

Avastin for Metastatic Breast Cancer

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The Technology

Bevacizumab (brand name: Avastin) is a recombinant humanized monoclonal antibody that binds to human vascular endothelial growth factor (VEGF), preventing its interaction with receptors on the surface of endothelial cells. Its effect is to stop angiogenesis, the development of new blood vessels—a process essential for cancer growth. Developed by Roche/Genentech, Avastin is widely used as an adjunctive therapy to traditional chemotherapies in the treatment of several types of cancers.

Rationale

There are approximately 230,000 new cases of invasive breast cancer in the United States annually and 40,000 breast cancer-related deaths.1 Approximately 29,000 newly diagnosed patients are already at stage IV at presentation, meaning that they have distant metastases. This group has a 15-percent five-year survival rate, based on National Cancer Database data from 2000 to 2001.2 As is true with many cancer types that present with distant metastases, few therapies have been identified that significantly improve survival once breast cancer reaches this stage. A cure is desperately sought.

Antiangiogenesis

In 1971, Judah Folkman of Harvard University hypothesized that angiogenesis was an important aspect of cancer biology and might be a target for future drug therapy.3 In the ensuing decades, with support from the National Institutes of Health’s (NIH’s) National Cancer Institute (NCI) and EntreMed, a biotechnology company in Rockville, Md., he began testing antiangiogenesis compounds in the laboratory setting. By the late 1990s, there was gathering excitement among researchers and the media about the promise of newer compounds for cancer coming from his lab. Citing developments in Folkman’s research, Richard Klausner, then the director of NCI, declared in 1998, “I am putting nothing on higher priority than getting this into clinical trials,” and Nobel laureate James D. Watson claimed that “Judah is going to cure cancer in two years.”4
Development

At the same time that the NCI was announcing Folkman’s breakthrough, a number of biotechnology companies and researchers were also pursuing antiangiogenesis drugs, albeit with less media attention. However, only Genentech had a drug that targeted a specific growth factor for angiogenesis: In 1989, a Genentech scientist named Napoleone Ferrara identified and cloned VEGF, the first specific growth factor to be described that promoted new blood vessel formation. In 1993, his team demonstrated that an antibody against VEGF could slow angiogenesis and tumor growth in a mouse model. Thus, while attention was focused on Folkman’s work, Genentech was quietly making progress. In 1995, it filed a patent for bevacizumab, an antibody against VEGF. By 1997, the first phase I clinical trial of the drug that would be brand-named Avastin began recruiting subjects.

From the outset, it was clear that Genentech believed Avastin was a potential blockbuster. The company not only spent hundreds of millions of dollars in research on angiogenesis to develop the drug; it decided to build a plant to manufacture Avastin before it received U.S. Food and Drug Administration (FDA) approval to market the drug in 2004. Priced at more than $4,000 a month (about $50,000 a year for metastatic colon cancer), Avastin generated sales of approximately $1.4 billion in its first full year after approval in the United States. Early sales and the promise for future growth for Avastin’s market attracted investors; between 2003 and 2005, shares of Genentech quadrupled.

In 2006 and in 2009, Avastin won FDA approval to use Avastin for some types of lung and breast cancer. The price of treating lung or breast cancer with Avastin is about twice as high as treatment for colon cancer because the drug is given at a higher dose for these cancers. The higher price point and growing use for multiple indications helped drive global sales as high as $6.2 billion in 2010. When the FDA subsequently revoked of approval of Avastin for breast cancer, sales dropped to $6.0 billion in 2011, but they rebounded to $6.1 billion in 2012, in part because of Avastin’s continued approval for use in metastatic breast cancer in Europe and Japan, and in part because of its expanded use to treat other forms of cancer.

Genentech’s research and financial successes attracted the attention of the giant Swiss global health care company F. Hoffmann-La Roche Ltd. (Roche), which in 1990 paid $2.1 billion to acquire a 56-percent share of Genentech. Executives at Roche explained their decision at the time by noting that Genentech’s pipeline was “the future of [Roche].” By 2009, with Roche’s income decreasing and Genentech’s net income skyrocketing due in large part to Avastin, Roche paid an eye-popping $46.8 billion to make Genentech a wholly owned subsidiary group.

Early Adoption

Initial FDA Approvals

The first FDA-approved use for Avastin in oncology came in 2004 after a successful phase III trial in metastatic colorectal cancer funded by Genentech. The addition of Avastin to chemotherapy as first-line treatment for metastatic colorectal cancer was shown to improve overall survival by about five months. Subsequently, additional FDA approvals were won for the second-line treatment of metastatic colorectal cancer (2006); first-line unresectable, recurrent,
Case Study 1: Avastin for Metastatic Breast Cancer

or metastatic non–small cell lung cancer (2006); second-line glioblastoma (2009); metastatic renal cell carcinoma (2009); and, later, other forms of cancer.\textsuperscript{16}

**FDA’s Emerging Regulatory Dilemma**

FDA approval of the use of Avastin in metastatic breast cancer was less straightforward than for other cancers. A clinical trial published in 2007 became the basis of FDA approval in early 2008. But by 2011, findings from subsequent trials prompted the FDA to withdraw its previous approval.

E2100, the clinical trial that was basis for the initial approval, was published in 2007. Funded by NCI, it was an open-label, randomized trial conducted by the Eastern Cooperative Oncology Group.\textsuperscript{17,18} Patients with newly diagnosed metastatic breast cancer who had not previously received cytotoxic drugs for metastases were eligible to participate. Patients with human epidermal growth factor receptor type 2–positive (HER2-positive) tumors, a marker for aggressive cancer, could only be included in the trial if they had previously received trastuzumab (Herceptin), Genentech’s antibody that specifically targets HER2. Patients were randomized to receive Avastin plus paclitaxel, versus paclitaxel alone.

Patients randomized to the Avastin group experienced an improvement in progression-free survival (PFS) of 5.5 months compared to those in the paclitaxel-alone group. This means that during this period, the disease did not seem to spread. However, Avastin-treated patients did not live any longer. In late 2007, the FDA’s Oncologic Drugs Advisory Committee (ODAC) met to debate whether the risk-benefit ratio of this trial supported making a recommendation to the FDA to approve Avastin.

Ralph D’Agostino, a voting member of ODAC, highlighted several concerns with using E2100 to support approval.\textsuperscript{19} First, E2100 was not designed to measure the outcomes on which FDA approval is usually based. Instead of overall survival, the trial was designed to measure PFS as its primary endpoint; the study made the more traditional outcomes measures, such as response rate, quality of life, and overall survival, secondary outcomes. Second, quality of life data were inconclusive, since the study was open-label and information on use of concurrent medications was not collected. Third, safety and toxicity data were not collected in the control group, making comparisons to the Avastin (treatment) group impossible. After considering these concerns, the ODAC voted 5–4 against approval, based on the lack of improvement of overall survival and uncertainty about other effects of the drug.

**Accelerated Approval**

Notwithstanding the ODAC’s concerns, the FDA granted accelerated approval to the drug in early 2008. The stipulation of “accelerated approval” meant that Genentech had to conduct additional studies to directly address the issue of overall survival. Only then would the agency grant standard approval.

**The FDA Reconsiders**

In June 2010, the ODAC met to consider additional evidence on the efficacy of Avastin as a treatment for metastatic breast cancer. Their primary reference point was the phase III Avastin and Docetaxel (AVADO) trial, which randomized patients to receive either docetaxel alone or in combination with different doses of Avastin. Although there were some signs of benefit from Avastin, such as tumor response, PFS improved by less than one month. As with the earlier
trial, there was no difference in overall survival. Even more concerning, patients randomized to the Avastin group had a higher incidence of serious adverse events.20, 21

Another phase III study, the Regimens in Bevacizumab for Breast Oncology-1 (RIBBON-1), showed similarly negative results: When Avastin was added to conventional chemotherapy, improvement in PFS was less than reported in the originally favorable trial, E2100; as with the other two studies, there was no improvement in overall survival. And like the AVADO trial, RIBBON-1 identified more serious adverse events in the Avastin group.22

With these new data in hand, the ODAC voted 12–1 to revoke FDA approval for Avastin in metastatic breast cancer.23 Genentech formally protested, citing four reasons why Avastin should remain approved: a lack of precedent for revocation of accelerated approval, the possibility that the drug might benefit subgroups, the importance of respecting individual choice in health care, and the possibility that the FDA's decision would discourage innovation.24 After considering Genentech's objections, in November 2011 the FDA revoked approval.

In her final decision memo, FDA commissioner Margaret Hamburg argued that data did not support Avastin's efficacy or safety for metastatic breast cancer. She also noted the lack of clinically meaningful benefit: No demonstrable improvement in survival had been reported in any of the studies, and an average improvement in PFS of a few months was not thought to be sufficiently meaningful to warrant the marketing of such a costly drug. Hamburg noted that Avastin did not improve quality of life; indeed, its use was associated with an increased risk of serious adverse events, including gastrointestinal perforations, wound healing complications, and hemorrhage. Taken together, she concluded, these findings suggested that Avastin did more harm than good for patients with metastatic breast cancer.25

In its decision to revoke Avastin's accelerated approval, the FDA noted that Genentech was free to pursue additional studies that might cause the FDA to grant new approval. Several authors and Genentech itself have noted that Avastin may have a role in treatment of metastatic breast cancer if biomarkers can be developed that identify a subgroup of patients who respond well to the drug or a combination of agents that boost Avastin's beneficial effects without causing added harm.

Public Backlash

Despite strong evidence supporting the FDA's action, many oncologists and cancer patients were outraged. All were convinced that Avastin appeared to be holding the cancers of some women at bay. Advocates for these women felt that the “FDA's blocking of compassionate access”26 was “nothing short of a death sentence.”27 Even the deputy chief medical officer of the American Cancer Society, J. Leonard Lichtenfeld, disagreed with the FDA decision, writing that he hoped insurance companies would still reimburse for Avastin for women “who are currently on the drug and who are showing a benefit from its use.”26 Opponents of health care reform, such as Sen. David Vitter (R-La.), argued that the FDA's revocation of its earlier accelerated approval was a prime example of the government “rationing access [to health care].”27

Subsequent Use

The story of Avastin's use for metastatic breast cancer underscores how policies influence a technology's adoption, uptake, and subsequent use. From the regulator's perspective, the story graphically illustrates the peril of using “accelerated approval” as a mechanism for getting a
high-priority drug, such as a cancer drug, to market. The FDA’s policy parallels in many respects the Centers for Medicare and Medicaid Services’ (CMS’s) “coverage with evidence development” policy for reimbursing promising but unproven technologies. Accelerated approval policies seek to speed the translation of promising research into practice, but they do so at the risk of raising false hopes about a technology’s benefits before they are clearly proven. Moreover, the FDA did not anticipate how difficult it would be to remove a product from the market or even restrict its use once it had developed a constituency among physicians and patients.

Perverse Economic Incentives
From the payers’ perspective, the Avastin story highlights several perverse incentives embedded in reimbursement policy for oncologic drugs, most notably that Medicare must reimburse even off-label (unapproved) use of drugs if they are listed in one of several drug compendia. Furthermore, the way oncologists are reimbursed (at a fixed percentage of the drug’s price) creates a perverse incentive to administer the most expensive drug for any indication in order to maximize practice revenue. This is because how much physicians are paid is calculated as a percentage of the drug’s price, not the difficulty of its administration. So even though the FDA revoked approval of Avastin for metastatic breast cancer in 2011, many doctors still use it to treat breast cancer patients, and Medicare still pays for its use.

Benefits and Risks of Accelerated Approval
The FDA created the option of granting “accelerated approval” based on surrogate endpoints to enable early approval of particularly important drugs and to add a measure of flexibility to the approval process. The accelerated approval mechanism was added to new drug application regulations in 1992, largely in response to pressure on the FDA to facilitate rapid deployment of promising treatments for HIV/AIDS.

Accelerated approval allows provisional approval of drugs that treat serious or life-threatening disease if they appear to provide benefit compared to other therapies. Benefit can be measured as an impact on a surrogate endpoint that is likely to predict clinical benefit. The applicant is obliged to perform confirmatory studies with due diligence to confirm the clinical benefit, at which point the drug can be converted to full approval if warranted by the evidence. If confirmatory studies are not performed with due diligence or the benefit is not subsequently proven, the FDA can revoke its accelerated approval.24 This is precisely what happened with FDA approval for Avastin to treat metastatic breast cancer.

The most recent review of accelerated approval in oncology by the FDA was published in 2011, before the final ruling on the fate of Avastin. At the time, 35 products had been granted accelerated approval for 47 indications in oncology, and only three had failed to prove some degree of benefit in confirmatory trials. Of the three, two were removed from the market, and one was allowed to be implemented with a limited distribution plan.28

Avastin for metastatic breast cancer became the fourth product to fail on confirmatory studies and the third to have its FDA approval revoked. Daniel Carpenter has argued that the decision to revoke affirmed the FDA’s credibility and established an important precedent that was, in his view, as important as the decision itself.24 Only by maintaining its independence and relying on available data in the face of philosophical and political criticism could the FDA affirm the integrity of its accelerated approval mechanism. However, the decision carried a political price—public criticism of the FDA for “rationing” care that was highly desired by patients who were convinced that it worked, irrespective of the data.
Use of Surrogate Endpoints as the Basis for Drug Approval

The Avastin story also illustrates the peril of relying on a surrogate endpoint in granting accelerated approval. The FDA is required by law to approve only drugs that show evidence of effectiveness. This requirement is based on a 1962 amendment to the Federal Food Drug and Cosmetic Act of 1938. After the amendment was enacted, effectiveness was defined in judicial rulings as having either a clinically meaningful benefit, such as improved survival, function, or symptoms, or an increased level of an established “surrogate endpoint.”

A surrogate endpoint is a laboratory measure or physical sign used as a substitute for a more clinically meaningful endpoint—for example, using average blood glucose control rather than survival to measure the effectiveness of a new treatment for diabetes. If a drug moves a surrogate endpoint in a favorable direction, it is assumed that this will translate into improved clinical outcomes.

Reasons to use surrogate endpoints, especially in trials treating metastatic disease, include the fact that patients tend to live longer than the duration of the trial and often receive many other types of chemotherapy, confounding measurement of a particular drug’s impact on overall survival. Surrogate endpoints in oncology over the past 30 years have included objective tumor response rates, disease-free survival, time to progression (TTP), and PFS. PFS, often used interchangeably with TTP, differs from the former because it is concerned only with progression rather than with both progression and death.

Despite a negative vote from the ODAC, the FDA based its accelerated approval of Avastin for metastatic breast cancer on the manufacturer’s use of PFS as its primary surrogate endpoint in the E2100 trial. Following the initial ODAC hearing on E2100, D’Agostino pointed out that use of PFS as an endpoint is fraught with problems. It not only requires blinding of radiologic evaluations, but its measurement and documentation depend on the timing of evaluations, which can be influenced by uneven assessment in different groups, missed assessments, and incomplete baseline measurements.

More difficult, perhaps, is the fact that some oncologists, patients, and advocates embrace such surrogate endpoints as PFS as meaningful outcomes themselves, regardless of the drug’s effect on actual survival. Richard Pazdur, the FDA’s director of the Office of Hematology Oncology Products, which is responsible for approval decisions, has been quoted as saying that delaying progression of disease “may be a direct clinical benefit in itself.” European oncologists are also inclined to believe that PFS is an important standalone endpoint, although it is difficult to support this view without concomitant evidence that a drug improves patients’ quality of life.

Use of surrogate endpoints in oncology is hotly debated. Recently, a new endpoint, pathologic complete response, has been proposed in the neoadjuvant setting of nonmetastatic breast cancer treatment. This refers to locally advanced cancers before surgical treatment. Two trials with Avastin using this surrogate marker have shown promise, and the FDA has agreed that the marker is “reasonably likely to predict clinical benefit” and therefore may be used. At the same time, however, the FDA has cautioned that the definition of the endpoint needs to be standardized, appropriate cancer subtypes and subgroups need to be refined, and the magnitude of surrogate improvement that correlates with overall survival must be determined.

Hope or False Hope?
The FDA’s accelerated approval policy and the companion CMS policy, “coverage with evidence development,” reflect the agencies’ genuine desire to provide access to promising new
technologies while remaining flexible with their subsequent approval and coverage decisions based on later scientific evidence. The policies are also similar in that they risk raising false hope that a technology is beneficial before benefit is clearly proven. The example of Avastin demonstrates that providing provisional approval to a drug may make it politically difficult to rescind approval later based on equivocal or contradictory evidence. The outcry from patients and physicians following the FDA's revocation of Avastin's approval for metastatic breast cancer suggests that the political costs of revoking approval, and dashing the hopes that approval raises, may be more problematic for the agency than requiring stronger evidence before allowing a drug to be brought to market.

The distinction between offering hope and false hope was cited by Mikkael Sekeres, a member of the ODAC, as a core reason for the committee's near-unanimous vote to rescind approval of Avastin. He argued that offering Avastin for metastatic breast cancer in the face of evidence that it is ineffective or even harmful amounts to providing false hope. Commenting on the danger of false hope, bioethicist Adrienne Martin has suggested that pharmaceutical companies can exploit the desperation of cancer patients by bolstering unreasonable hope of a highly unlikely outcome. Specifically citing Avastin for metastatic breast cancer, she noted that "fear of death, fear of cancer, hope for cure . . . all of these and more make cancer patients overvalue the promise of five additional months free of disease progression."40

**Mandated Payment for “Off-Label” Use**

Shortly before the FDA revoked its accelerated approval of Avastin for metastatic breast cancer, the National Comprehensive Cancer Network (NCCN) added Avastin to its Compendium of Drugs and Biologics for this indication. This decision meant that even if FDA approval were subsequently revoked, CMS would remain legally bound to reimburse use of Avastin for metastatic breast cancer, including paying medical oncologists their drug administration fee. Put another way, revoking FDA approval for metastatic breast cancer did not remove the drug from the market; it simply meant that Genentech could no longer promote its use for metastatic breast cancer. Medical oncologists who wanted to keep administering it for this condition could do so, and CMS would pay.

CMS reimbursement of off-label use of cancer drugs is far more common than people realize. Indeed, the NCCN estimates that 50–75 percent of all cancer drugs are administered off-label.41 This peculiar approach to reimbursement is written into federal law. The Social Security Act of 1993 required that Medicare reimburse all anticancer drugs and biologics listed in certain compendia, such as the NCCN. In 2008, five such compendia met CMS criteria.42 In addition, nearly three-quarters of the U.S. population live in states that require private insurers to cover certain cancer drugs. Laws in most of these states mandate that plans must pay if a prescribed drug is listed in a recognized compendium, irrespective of FDA approval. Some states mandate insurance coverage if a drug is simply mentioned in the peer-reviewed literature.43

Amy Abernathy has argued that drug compendia such as the NCCN’s are given disproportionate weight in deciding the appropriateness of off-label prescribing. By requiring reimbursement of any drug listed in one of these compendia, Congress and the states are essentially relying on the organizations that publish them to perform comparative-effectiveness research, although that is not their purpose and they lack the resources to do it. Furthermore, the subjective processes and lower levels of evidence used by different compendia compromise the valid-
ity of their assessments. In the case of Avastin, one-third of NCCN’s breast cancer panel had financial ties with Genentech. The company also funds the NCCN directly.25

Abernathy has suggested that one way to address the issue of regulatory approval for off-label use is to require continuous evidence collection and reevaluation of a drug’s use, much as the FDA and CMS seek to authorize products with provisional approval today. Another potential strategy is to require “pragmatic” clinical trials that use real-world populations and comparators and measure clinically relevant outcomes, thereby learning from evidence collected in actual clinical practice. As matters stand, once a compendium adopts a drug, Medicare and other insurers must pay for its use, irrespective of FDA approval or the subsequent generation of contradictory clinical evidence.

Physicians Are Rewarded for Using the Most Costly Drug
Before 2005, reimbursement for Part B cancer drugs, which are typically physician-dispensed and are mostly chemotherapeutic agents, was pegged at 95 percent of a drug’s average wholesale price. Manufacturers competed for market share by offering discounts to purchasing physicians so that they could increase the margin between what they paid to purchase the drug and what they received in reimbursement. Because the prices of most of these drugs were set quite high, paying the administering physician 95 percent of the product’s listed wholesale price gave doctors a hefty margin, since manufacturer discounts (often 12–30 percent, but as high as 86 percent) meant that they were paying far below list price for these drugs.45

In an attempt to reduce these high dispensing margins and rein in Medicare spending, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 changed reimbursement for Part B drugs to the manufacturer’s average sales price (ASP) plus 6 percent and an administrative fee. Although this change decreased Part B drug reimbursements, of which chemotherapy drugs are the majority, on the short term, it created a perverse incentive for manufacturers to charge the highest price possible for their drugs, because this meant that physicians who used them made more money (6 percent of ASP) than if they treated their patients with less-expensive drugs.45, 46

The ASP plus 6 percent rule quickly altered the behavior of manufacturers. They began to set high initial launch prices, rather than raising their prices after release as they had before. This was done because there is a two-quarter lag in adjusting the ASP. Additionally, for compounds that can be dispensed by both physicians and pharmacies, perverse pricing of Part B drugs created a “spillover” effect on pharmacy prices, since manufacturers are likely to charge the same price in both settings. Although the 20 percent patient co-pay required from patients for Part B drugs had the potential to cause sticker shock, this proved not to be a major barrier to high pricing, since most Medicare patients purchase supplemental Medigap coverage or are dually eligible for Medicaid. Those who lacked supplemental coverage went without. Finally, because private insurers often follow Medicare’s lead on payment policy, the ASP plus 6 percent rule quickly drove the entire market in physician-dispensed drugs.46

Once Approval Is Granted, the FDA Has Limited Power to Discourage Use of a Low-Value Treatment
Securing regulatory approval is a high bar to clear. But once approval is secured and a drug has the opportunity to establish itself in the minds of doctors and patients, it can be shielded as well. This is particularly true for cancer drugs. Because CMS and many private insurers are legally obliged to reimburse the off-label use of Avastin for metastatic breast cancer irrespec-
tive of the FDA’s subsequent revocation of approval, the agency could not stop practitioners from prescribing the drug for this condition. There is, however, some evidence that the agency’s decision to revoke approval blunted use. Genentech reported that by the end of 2011, when the FDA’s final decision to revoke approval was announced, use of Avastin for metastatic breast cancer declined from 60 percent of eligible patients to 20 percent. At an IOM workshop in 2012, United Healthcare reported that by encouraging providers to follow medical evidence, they cut use of Avastin for this now unapproved condition in half between 2009 and 2012.

Cost and Health Impact

Despite paying more than $8,000 a month for the treatment, patients who receive Avastin for metastatic breast cancer do not live longer than patients treated with other chemotherapeutic regimens. They also have a significantly higher risk of life-threatening complications, such as gastrointestinal perforations, wound healing complications, and hemorrhage. This is a high price to pay for one or two additional months of PFS without measurable improvements in quality of life.

Since the FDA revoked its earlier approval, more specific evidence about the cost effectiveness of Avastin for metastatic breast cancer has been developed. An independent group performed a cost-effectiveness analysis using data from the three big clinical trials of Avastin for metastatic breast cancer: E2100, AVADO, and RIBBON1. Because Avastin does not extend life, E2100 data showed an incremental cost of $100,300 to add 0.49 years of PFS, which equates to 0.135 quality-adjusted life years (QALYs). (QALYS are a measure of disease burden that includes both the quality and the quantity of life lived.) The calculated incremental cost-effectiveness ratio (ICER) was therefore $745,000 per QALY, an astronomical sum. RIBBON1 showed that adding Avastin to the chemotherapy agent alone led to an increase of 0.168 QALYs, at an ICER of $425,000 per QALY. AVADO showed an increase of 0.0375 QALYs, at an ICER of $1,937,000 per QALY.

Thus, by any measure, Avastin is not cost-effective for the treatment of metastatic breast cancer. Using E2100 data and a threshold of $150,000 per QALY, the price of the drug would have to be cut by 80 percent, or PFS would have to be boosted by ten months, to make Avastin reasonably cost-effective compared with other treatment options.

In a 2006 interview, the company’s president of product development defended the product’s high price, based on “the value of innovation, and the value of new therapies.” Roche/Genentech’s annual report in 2010, issued in the midst of FDA decisionmaking about Avastin, further explained the company’s mindset: “... we consider it vital for the future that policymakers and health officials look not only at the costs of new medicines but also at the innovation they embody and the benefits they offer patients... medical progress should be viewed more as a public good that deserves vigorous political support.”

The Regulator’s Dilemma

Judah Volkman’s discovery did not cure cancer, but the technology it inspired has generated billions in sales for Genentech and Roche. The FDA’s experience with Avastin illustrates the difficult balancing act the agency must maintain between those who think it moves too slowly
and those who criticize it for hasty decisions. The FDA granted Avastin accelerated approval for use in metastatic breast cancer on the basis of a single clinical trial that used a surrogate endpoint, with the understanding that further studies would be done. By the time that this additional research showed that Avastin does not increase survival or improve the quality of patients with metastatic breast cancer, the drug had built a loyal following among oncologists and cancer patients who felt otherwise. Moreover, during the relatively brief time period in which Avastin held accelerated approval, it secured a spot on a major drug compendium. Because Avastin is included in the compendium, federal law requires Medicare to keep paying for doctors to administer this highly expensive and potentially harmful drug for a condition it does not help, even though the FDA subsequently revoked its approval of Avastin for use in metastatic breast cancer. Thus, policies and decisions implemented for the best of reasons can ultimately generate substantial costs without improving human health.

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The Technology

There is no single definition of the cardiovascular polypill. The term generally refers to a multidrug combination pill intended to treat multiple physiological variables that increase the risk of developing cardiovascular disease. In 2000, Wald and Law secured an EU patent for a cardiovascular polypill consisting of aspirin, an intermediate-dose statin, folic acid, and three antihypertensive medications at half-dose. The first public description of the idea was published in 2003. Subsequent and ongoing studies and clinical trials have employed polypills with somewhat variable components, but most include aspirin, a statin for lipid-lowering, and several low-dose antihypertensive medications from different therapeutic classes (i.e., diuretic, angiotensin-converting enzyme inhibitor, beta-blocker, and/or calcium channel blocker).

Rationale

Cardiovascular disease is the leading cause of morbidity and mortality in the United States and around the world. In the developing world, the burden of cardiovascular disease has decreased; however, these gains are seriously threatened by growing prevalence rates of obesity and diabetes mellitus. In developing countries, the toll of cardiovascular disease remains unchecked; by the year 2020, 80 percent of global cardiovascular morbidity and mortality is projected to occur in low- and middle-income countries. Many of the risk factors that lead to cardiovascular disease and have been identified in rigorous epidemiologic analyses are modifiable through lifestyle interventions and pharmacologic therapy, including hypertension, hyperlipidemia, insulin resistance, and smoking. Many drugs have been shown through randomized trials to be efficacious both at reducing these important risk factors and also at lowering the rate of major adverse cardiovascular events. Therefore, the hope of attenuating the global burden of cardiovascular disease rests, at least in part, on successful deployment of affordable pharmacotherapy.

Efforts to manage cardiovascular disease in the developing world have been limited for myriad reasons, including high costs and poor adherence to complex medical regimens, inconsistent utilization of highly effective secondary preventive pharmacotherapy, and suboptimal risk stratification for primary prevention of cardiovascular disease. A cardiovascular polypill, consisting of aspirin, statin, and three antihypertensive medications, could potentially represent a simple, easy, and affordable intervention to overcome many of these barriers.
Although the idea of an inexpensive cardiovascular polypill is particularly well-suited for the developing world, it would also be useful in the United States, which has rates of obesity and type II diabetes that are among the world’s highest, as well as tens of millions of people with poorly controlled hypertension. Many of these cases are either unrecognized or undertreated, although it is widely known that hypertension increases the risks of heart disease, stroke, and kidney failure—all leading causes of death, long-term disability, and health care spending. Despite this knowledge, the Centers for Disease Control and Prevention estimate that fewer than half of the 68 million Americans with high blood pressure are on an adequate regimen of treatment.8

The specific rationale for the polypill depends on the population to which it would be applied. For primary prevention, the polypill approach essentially obviates the need for sophisticated and expensive risk stratification tests. Instead, it would be recommended for all individuals older than a specific age—55 or 60, for example—rather than using multiple risk factors to identify candidates.9 This is attractive because rather than tailoring treatment toward those at highest risk, a simple intervention would be applied to the broad population that accounts for a large proportion of adverse events.10 An added justification is that the relationship between the severity of risk factors and the incidence of serious adverse events is continuous, not a threshold phenomenon.11 Moreover, age has a much greater discriminatory effect on predicting the risk of heart attack and stroke than do such physiological risk factors as hypertension and hypercholesterolemia, as important as the latter factors are.39

Applied to secondary prevention, the case for a polypill is equally, if not more, compelling. Aspirin, beta blockers, statins, and angiotensin-converting-enzyme (ACE) inhibitors are already used for secondary prevention; each has been shown in numerous, large, randomized clinical trials to significantly reduce the incidence of cardiovascular deaths, myocardial infarction, and stroke. Significantly, each treatment is professionally endorsed with Class I, Level of Evidence A recommendations in clinical practice guidelines.12 In fact, it is estimated that about half of the reduction in cardiovascular disease burden in developed countries like the United States is attributable to advances in medical therapy.13

Unfortunately, guideline-indicated medications are not prescribed to all individuals for whom they are indicated. Moreover, even when properly prescribed, adherence to complex and costly multidrug regimens is distressingly low: about 50 percent.14, 15 If a cardiovascular polypill could be developed that simplifies care delivery, lowers costs through use of generic drugs, and improves adherence by packaging the benefits of multiple effective drugs into a single pill, it could have far-reaching implications for reducing the burden of cardiovascular disease in both high- and low-income countries worldwide.

Development

Multiple polypills have been created over the past decade, most resulting from collaboration between academic researchers and drug manufacturers. Although there are approximately 50 two-drug combinations for treating hypertension that have received approval from the U.S. Food and Drug Administration (FDA) or other regulatory agencies, a cardiovascular polypill containing three, four, or even five drugs has not been reviewed by any regulatory authority and, thus, is not commercially available. Because the polypill has not been evaluated with a large-scale randomized trial involving clinical endpoints, it has no chance of gaining
regulatory approval in the United States for primary prevention of cardiovascular disease. In the developing world, it might be possible to bypass the conventional national-level approval process and appeal to the World Health Organization to place a cardiovascular polypill on the Essential Medicines list. Another option, used by Polypill Ltd in the UK, is to offer the public access to an unlicensed pill, provided that it is prescribed by willing clinicians.16

The intellectual property issues surrounding the polypill deserve mention. Several patent applications have been filed, including the original one by Dr. Wald and Dr. Law in 2000 (GB2361186).1, 17 Normally, the granting of a patent facilitates bringing a product to market by providing some chance of recouping the large investment involved, perhaps hundreds of millions of dollars, to develop a product, secure regulatory approval for its sale, and manufacture it in a consistent and safe way. Cipla Limited, a pharmaceutical company based in Mumbai, India, is currently manufacturing a polypill based on the work of Wald and Law.

Early Adoption

The polypill has been tested in several phase II clinical trials (smallefficacy and safety trials evaluating intermediate endpoints, such as low-density lipoprotein cholesterol [LDL-C] or blood pressure) and a few modest-sized phase III trials (larger outcomes trials evaluating safety and efficacy on such clinical endpoints as death, myocardial infarction, and/or stroke). Several trials are still under way.

The need for further trials is a matter of debate. Critics argue that the safety and efficacy of a cardiovascular polypill has not been conclusively demonstrated with a large phase III randomized trial. Advocates of the polypill note that its various ingredients have been extensively tested and are known to be safe and effective. Moreover, many of these drugs are safely prescribed together at doses higher than those used in a polypill. For this reason, they question whether further trials are needed, given the existing evidence. Nevertheless, under existing FDA policy a combination pill must demonstrate efficacy and safety for its intended use as if it were a new chemical entity, even if the individual drugs it contains have been previously approved and are frequently prescribed together.

Subsequent Use

More than a decade has passed since the concept was proposed. Although an effective polypill could have an immense impact on the burden of cardiovascular disease, it is little closer to entering mainstream practice than the day it was first described. What is hindering its development and adoption?

No Consensus About the Pill’s Components, Target Population, or Commercial Viability

Critics offer several concerns, beginning with the polypill’s conception and extending to its development and potential deployment:18

1. There is no consensus on what constituent drugs should be included in the combination therapy, no consensus regarding the target population that would receive it, and
no consensus regarding the principal objective for its use (primary and/or secondary prevention).

2. Some worry that there are important pharmaceutical formulation issues related to bioavailability, pharmacokinetics, adverse drug–drug interactions, and other problems that combination therapy might engender.19

3. Investors might question the medication’s patentability and the profitability of marketing a low-cost, prevention-oriented pill in the current health care marketplace.

4. If a cardiovascular polypill were offered in the U.S. market, it is far from clear that providers would embrace it. Many clinicians might resist the notion of abandoning individualized care, which involves the development and meticulous titration of a customized treatment plan, in favor of prescribing a polypill.20

5. Some express concern that using a polypill for primary prevention of cardiovascular disease would “medicalize” prevention and create a moral hazard that would dampen patients’ desire to make meaningful lifestyle modifications.21

6. Some assert that, regardless of the strength of evidence on the safety and efficacy of the pill’s individual components, marketing should not be allowed unless data are generated in large phase III clinical trials to prove that a cardiovascular polypill is efficacious and safe.

Costly Phase III Clinical Trials Required for Regulatory Approval
Irrespective of the polypill’s intuitive appeal and strong epidemiological rationale, regulators and health care providers will expect robust evidence that it works before supporting its use in clinical practice. The “burden of proof” will vary depending on the clinical circumstance. In the simplest scenario, in which a patient on costly multidrug regimen switches to a polypill containing the same (or closely related) ingredients, an outcomes trial might be unnecessary. However, since the polypill is envisioned for first-line therapy of patients with hypertension and/or type II diabetes rather than “therapeutic consolidation,” costly phase III outcomes trials may be required. The same considerations will apply if the drug is envisioned for primary prevention of cardiovascular disease in people above a given age.

Even if outcome studies show that a polypill is effective, opponents will note that a key rationale for the polypill, nonadherence to guideline-recommended multidrug therapy, is multifactorial in etiology. Clearly, therapeutic complexity (multiple drugs, multiple daily administrations, etc.) and cost are important contributors to nonadherence, but they are not the only factors. Even a simple once-a-day polypill will not address the social, cultural, and behavioral factors that contribute to nonadherence.22 Findings from clinical trials conducted to date have reported discontinuation or incomplete follow-up rates ranging from a low of 2.2 percent to 27 percent.23 24 25 This variability suggests that even a simple, once-a-day tablet such as the polypill is not a panacea for nonadherence.

Proponents of the Polypill See Large Potential Benefits
Defenders of the polypill argue that most of these objections have no merit. They note, for example, that reaching clinical consensus over the components of the polypill is irrelevant; all that matters is finding an effective combination of drugs that can be safely administered in a once-a-day pill. They note that the pharmacology of the various components is well-known and that hundreds of thousands of patients are already prescribed complex multidrug treat-
ments at far higher doses than anything envisioned for a polypill. They could also point out that physicians’ resistance to abandoning “individualized care” has at least as much to do with financial self-interests as concern for patients, many of whom are inadequately treated at the present time. They note that although modifying harmful lifestyles is an important goal, this strategy is largely failing. Moreover, medical prevention should not be viewed as competing with lifestyle improvement; the two are complementary.

Given the enormous burden of ischemic heart disease and stroke in the U.S. population, achieving even a modest decrement in the main causal factors of cardiovascular disease would prevent a huge number of cardiovascular-related deaths, diseases, disabilities, and health care costs.

There Is Little or No Market for a Cost-Saving Pill

Because the current economics of drug development reward the creation of patentable products that can command high prices, there is no market rationale for spending large sums of money to secure FDA approval of a less-expensive pharmaceutical, even one that is patented and could replace or sharply reduce demand for more-expensive medications. For this reason, it is unlikely that any pharmaceutical firm, no matter how wealthy, will invest the sums of money required to fund the multicenter phase III trials that would be required to gain regulatory approval, regardless of the polypill’s potential value to patients and society at large.

Cost and Health Impact

Wald and Law, who first proposed a cardiovascular polypill, postulated that it could reduce the global burden of cardiovascular disease by about 80 percent.2 This was based on an estimate that lowering cholesterol would reduce the risk by about 30 percent, lowering blood pressure would reduce risk by another 30 percent, inhibition of platelet activation and aggregation would reduce risk by about another 25 percent, and an additional 16 percent reduction in mortality could be achieved with folic acid. However, there are two limitations to their analysis. First, use of folic acid has not been shown to improve outcomes in a large, randomized trial.26 In addition, although aspirin is the cornerstone of antiplatelet therapy for the secondary prevention of cardiovascular disease, its use in primary prevention is more questionable because of the risks it poses for bleeding.27 Due at least in part to the widespread prescribing of statins, baseline levels of total cholesterol and LDL-C have dropped in the decade since Wald and Law’s initial publication. Therefore, the projected reductions in LDL-C and severe adverse cardiovascular events they postulated have recently been amended.28 Even so, likely preventive effects are still large. Also, although the epidemiologic evidence linking reduction of elevated blood pressure with clinical benefit is irrefutable, some argue that there is no evidence to support the administration of multiple low-dose antihypertensive agents to patients who do not have documented hypertension but are at risk for developing the condition.29, 30 This view has been refuted by a large meta-analysis.31

Notwithstanding these concerns, most experts believe that a multidrug combination pill that simplifies care delivery, reduces costs through use of generic drugs, and improves adherence would have far-reaching implications for reducing the global burden of cardiovascular disease. Even if Wald and Law’s projected benefits are reduced somewhat by omitting folic acid and aspirin, an intervention that cut the global burden of cardiovascular disease by even half
the magnitude that they project would have an enormous impact on morbidity, mortality, and health care spending.

**Small-Scale Trials Have Produced Promising but Inconclusive Findings**

The Indian Polycap Study (TIPS) was the first published. Funded by the St. John’s Research Institute (Bangalore, India), the Population Health Research Institute (Hamilton, Canada), and Cadila Pharmaceuticals Ltd., it enrolled 2,053 individuals aged 45 to 80 years with at least one risk factor but without overt cardiovascular disease. An unfortunately complex allocation scheme was used to randomize patients to receive the “polycap” (thiazide 12.5 mg, atenolol 50 mg, ramipril 5 mg, simvastatin 20 mg, and aspirin 100 mg) or to one of eight other groups that included single drugs or various drug combinations. There was no true placebo group, just three monotherapy arms with aspirin, thiazide, or simvastatin. Compared with subjects who were randomized to treatment arms that did not include antihypertensive therapy, the polycap reduced blood pressure by 7.4 mm Hg systolic and 5.6 mm Hg diastolic. In another analysis that compared patients who were prescribed atenolol or simvastatin to those who were not, the polycap lowered heart rate by 7.0 beats per minute and LDL-C by 0.73 mmol/L, respectively. The degree of platelet inhibition achieved with the polycap was similar to that achieved with aspirin alone.

The rate of noncompliance in the various treatment arms was approximately 15 percent over the three-month follow-up period, a little less than a third of which (4 percent) was due to side effects. Based on these results, the authors projected that widespread and sustained use of the polycap could reduce the risk of ischemic heart disease by 62 percent and stroke by 42 percent.

Following the publication of these findings, the funders of the first TIPS study sponsored a second polycap study, TIPS-2. This time, investigators randomized 518 subjects with previous vascular disease and/or diabetes to one polycap versus two polycap pills, thereby testing “half-dose” versus “full-dose” therapy. As before, there was no placebo group. The group randomized to two polycap pills had additional, significant reductions in systolic and diastolic blood pressure, LDL-C, and total cholesterol without any incremental changes in mean heart rate or HDL-C. The discontinuation rates at eight-week follow-up were similar in both groups: about 8 percent.

In 2012, the inventor of the polypill and two colleagues reported the results of a randomized double-blind placebo-controlled crossover trial of a polypill among 86 subjects aged 50 or above without a prior history of cardiovascular disease. To assess the accuracy of their prior models, they compared observed reductions in blood pressure and low-density lipoprotein (LDL) with those predicted from published estimates of the effects of the individual drugs. Participants took a once-a-day polypill containing amlodipine 2.5 mg, losartan 25 mg, hydrochlorothiazide 12.5 mg, and simvastatin 40 mg for 12 weeks and a placebo for 12 weeks; the order of treatment was randomly assigned. Each subject’s mean within-person difference in blood pressure and LDL cholesterol was measured each 12-week period. Eighty-four subjects completed both treatment periods, a compliance rate of 98 percent. The polypill reduced mean systolic blood pressure by 17.9 mmHg, diastolic blood pressure by 9.8 mmHg, and LDL cholesterol by 1.4 mmol/L (1.2–1.6). The observed reductions were almost identical to those predicted. Long-term reductions of this magnitude would be expected to have a substantial impact on the incidence of heart attacks and strokes. In 2003, a fourth study, the Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE) trial, was published in the *Journal*
of the American Medical Association. It is part of a larger collaborative effort called the Single Pill to Avert Cardiovascular Events (SPACE) program, which is being supported by Imperial College London; the George Institute in Sydney, Australia; and Dr. Reddy’s Laboratories Ltd. The SPACE program includes the Kanyini Guidelines Adherence with the Polypill (GAP) study and the Improving Adherence Using Combination Therapy (IMPACT) trial, which is being conducted in New Zealand.

UMPIRE randomly assigned 2,004 patients to a polypill containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and either atenolol 50 mg or hydrochlorothiazide 12.5 mg versus usual care (which might or might not involve use of similar prescription drugs, so it was not a “pure” placebo group). Most of the study subjects had established cardiovascular disease; 28 percent were diagnosed with type II diabetes. At the completion of the 15-month study, 86 percent of patients in the fixed-dose combination study arm were still taking the medication, compared with 65 percent in the usual-care arm, a statistically significant improvement in adherence. This translated into a 4.2 mg/dL reduction in LDL cholesterol levels and a 2.5 mmHg reduction in systolic and diastolic blood pressure—relatively modest but still clinically important differences.

Two other prospective studies of cardiovascular polypills are ongoing: the International Polycap Trial 3 (TIPS-3), sponsored by Wellcome Trust (United Kingdom) and Cadila Pharmaceuticals Ltd., and the Heart Outcomes Prevention Evaluation 3 (HOPE-3) study, funded by Astra Zeneca and the Canadian Institutes of Health Research.

TIPS-3 (NCT01646437) plans to enroll at least 5,500 participants (women 60 years or older and men 55 years or older) without known heart disease or prior stroke, with a planned follow-up period of five years. Subjects will be randomized in a 2x2x2 factorial design to polycap DS (thiazide 25mg, atenolol 100mg, ramipril 10mg, simvastatin 40mg) versus placebo, aspirin 75 mg versus placebo, and cholecalciferol 60,000 IU monthly versus placebo. The study is powered to detect important differences in major adverse cardiovascular events.

HOPE-3 (NCT00468923) is not evaluating a polypill per se, but rather rosvastatin 10 mg or placebo and combination candesartan 16 mg/hydrochlorothiazide 12.5 mg versus placebo in a 2x2 factorial study. It is projected to enroll 11,000 subjects (women 60 years or older and men 55 years or older) from 21 countries who have no known heart disease or prior stroke. Thus, it is oriented around primary prevention. This study is also powered to detect important differences in major adverse cardiovascular events. It is projected to be completed in 2015. If these studies generate favorable results, they could prompt health ministries in developing countries to embrace the concept and perhaps stimulate additional interest in the United States.

These findings beg the question: How much evidence is needed to support the adoption of a polypill in the United States? Given the enormous cost of large-scale phase III trials and substantial evidence of the polypill’s efficacy and safety among patients at risk for serious consequences of cardiovascular disease, is more research needed? For capitated health systems, which have a strong interest in achieving better health at lower cost, the answer may be “no.”

Recently, Kaiser Permanente Northern California (KPNC) published the results of a comprehensive program to improve blood pressure control among its members. The authors reported that the program achieved “a significant increase in hypertension control compared with state and national control rates.” Key elements of KPNC’s program, as reported by the authors, included “a comprehensive hypertension registry, development and sharing of performance metrics, evidence-based guidelines, medical assistant visits for blood pressure measure-
ment, and *single-pill combination pharmacotherapy*” (emphasis added). The pill employed by the program contains only two agents—hydrochlorothiazide and lisinopril—so it is technically not a polypill. Even so, the authors noted that “Single pill combinations have important advantages, including improved adherence, and lower patient cost, and are associated with improved blood pressure control.”

Based in part on the success of this effort, Kaiser Permanente has launched the ALL initiative (named for the systematic use of aspirin, lisinopril, and lipid-lowering medication). The organization’s goal is to reduce the incidence of heart attacks and strokes among its members through secondary prevention. Kaiser has also rolled out the PHASE program (Preventing Heart Attacks and Strokes Everyday), which seeks to build on ALL by adding a beta blocker to the regimen and encouraging healthy lifestyle changes. If Kaiser Permanente achieves the outcomes it seeks with these initiatives, it could open the door for other capitated health systems to follow. In that case, the simplicity of using a polypill to advance secondary or even primary prevention could be an appealing option.

**Development Block**

The cardiovascular polypill is an example of “development block.” Despite the fact that this promising technology offers the prospect of tremendous value to society in terms of health benefits per dollar spent, its pace of development is slow. This appears to be largely due to the lack of a compelling business model, given the current way new drugs are patented, regulated, and reimbursed. If, as the polypill’s proponents assert, individuals could cut their risk of sustaining a stroke or developing ischemic heart disease by half or more simply by taking an inexpensive once-a-day pill with few or no side effects, it is likely that millions of people would choose to do so. However, there is no obvious path for the inventors of the polypill to get from “here” to “there.”

The polypill’s advocates note that its various components have been extensively studied and are highly efficacious. All are approved for sale, provided that they are individually prescribed and swallowed as individual pills. Several antihypertensive pills are marketed as two-drug formulations. The epidemiological and clinical trial data on the potential benefits of combination therapy are impressive. Short-term clinical trials of the polypill have produced reductions in blood pressure and LDL cholesterol comparable to those achieved in prior, individually dosed clinical dose trials. Side effects were uncommon, as might be expected given the low doses involved. If the physiological improvements observed in these studies were sustained over time, treated subjects should have far fewer cases of heart attack and stroke. The benefits this would produce—both in terms of human health and health care spending—would be profound.

For the same investment pharmaceutical firms routinely make to test a promising diabetes medication or a new cancer drug, a polypill could be rigorously evaluated through a large phase III randomized trial involving tens of thousands of subjects. If demonstrated to be safe and effective at preventing ischemic heart disease and strokes, the benefits of promoting this treatment would dwarf the development costs of getting a polypill to market. The problem is that under the current structure of pharmaceutical markets and regulators, the financial benefits of the polypill would be realized by patients, payers, and perhaps capitated health care systems, not the pill’s developer or the doctors who prescribe it.
As long as the regulatory costs to enter the U.S. market are as high as they are, the drug development market will remain aligned to reward the creation and marketing of high-priced pharmaceuticals. In that case, it is unlikely that we will see much work on such dramatically cost-lowering drugs as the cardiovascular polypill.

No one knows how many promising drugs, biologics, devices, and diagnostic technologies are languishing on the fringes of our health care marketplace. But a process recently embraced by the Office of Science & Technology in the Department of Homeland Security (DHS) might be useful way to identify interesting ideas. The approach, known as “technology foraging,” was envisioned to help DHS identify existing but largely overlooked inventions that can be swiftly adopted or repurposed to meet urgent agency needs. If the U.S. Department of Health and Human Services or a large integrated health care delivery system, such as Kaiser Permanente, the Veterans Healthcare Administration, or the Military Health System, adopted a similar approach, it might be possible to identify and evaluate promising health care technologies that offer the potential for dramatic benefits at far lower cost than the options we have today.

References


The Technology

Electronic health records (EHRs) include a variety of medical documentation systems “generally focused on medical care,” including patient information, diagnoses, procedure codes, and medications. There are many types of EHRs, ranging from hospital systemwide records, ambulatory care records, emergency department records, and medication administration documents. EHRs are often called electronic medical records (EMRs). The latter is a legal record documenting the patient encounter and clinical services and is typically controlled by the hospital or care delivery organization that generates it. For this review, we use the term EHRs because they encompass more types of medical data.

Rationale

EHRs were developed in response to the needs of a range of stakeholders in the health care system. Because paper charts are often illegible, have missing data, are difficult to organize, occupy substantial physical space, are sometimes misplaced or lost, and are difficult to share, stakeholders immediately grasped the potential of using computers to store, retrieve, and process medical record data faster than any paper chart. Initially, the Office of Data Management and Telecommunications sought computerization for administrative and research purposes on a national level; locally, Veterans Affairs (VA) medical centers looked to computerization to improve their efficiency and quality of care. Likewise, academic medical centers sought to “utilize the speed, efficiency and reliability of digital computer processing” to collect, store, and retrieve patient data.

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Development

EHRs were envisioned as early as the 1950s, with the testing of computer-based medical histories. In the mid-1960s, Dr. Lawrence Weed, inventor of the “problem oriented medical record,” and others began working on electronic versions of a patient’s medical record that allowed clinicians to focus on manageable bits of information that would be easily computerized and retrieved. During the same period, several academic institutions developed computer-based patient records, including hospital and office-based medical record systems.

In the 1960s and 1970s, with support from the National Center for Health Services Research and Development and the Denver Department of Health and Hospitals and Beth Israel Hospital in Boston, early medical information systems were developed. The Latter Day Saints Hospital and the University of Utah received funding from the Regional Medical Program to expand its prototype health information system beyond research purposes. The Massachusetts General Hospital System secured grants from the National Institutes of Health (NIH), the National Center for Health Services Research and Development, and a contract funded jointly by the NIH and the American Hospital Association to establish its computer facilities and sponsor the development of computerized hospital records.

Early Adoption

Almost as soon as EHRs were developed, new capabilities were added, including providing clinicians with access to data from multiple caregivers, clinical decision support to improve the management of complex patients, and the capability to track the process of care and outcomes. In the 1980s, a time when several health care systems were organizing themselves into health maintenance organizations (HMOs), providers were expected to accurately document their care so that it could be evaluated for quality, outcomes, and cost. This drove early adoption of EHRs and broadened their uptake.

The federal government encouraged adoption by providing some funding for computer-based patient records projects, but most health systems self-funded their EHRs. By 1991, early adopters were reporting a range of benefits, including lower costs, shorter inpatient stays, improved outcomes, and fewer medical errors.

In 2000, To Err is Human, the Institute of Medicine’s (IOM’s) landmark report on medical error, provided additional impetus for the adoption of EHRs. In addition to describing the magnitude and dimensions of medical error, the IOM proposed solutions. One of its major recommendations was that health care providers and systems use EHRs and other computer-based systems to reduce medical errors and improve the quality of care.

Subsequent Use

In 2004, the George W. Bush administration initiated a push to transition the nation from paper to electronic medical records. To jump-start the process, the administration requested a doubling of federal funding for health information technology (HIT) and created the position of the national health information coordinator (later renamed the national coordinator for
health information technology [IT]). Congress did not approve the administration’s funding request, but the establishment of the Office of the National Coordinator for Health IT set the stage for what was to follow.

Studies Identify Potential Value
The next big push for EHR adoption came in 2005, when a team of RAND researchers published a major analysis of the potential economic payoffs of widespread adoption of HIT.19 Using sophisticated models based on empirical observations of IT adoption in other sectors of the U.S. economy, RAND’s team projected that if “interoperable and interconnected [electronic medical records] are widely adopted and used effectively,” the United States could save more than $81 billion annually through improved efficiency and enhanced patient safety. The Center for Information Technology Leadership reached similar conclusions about the potential value of health information exchanges.20

Despite these optimistic predictions of benefit, adoption of EHRs lagged. In 2008, a national survey of 2,758 physicians revealed that just 4 percent had a fully functional EHR, and 13 percent had a basic system. Although these early adopters were few, they reported positive effects of the systems on several dimensions of quality of care and generally high levels of satisfaction with their systems. Financial concerns were viewed as the biggest obstacle to adoption.116

HITECH Provides Financial Incentives for Adoption
In 2009, the stimulus funding provided through the American Recovery and Reinvestment Act (ARRA) provided an opportunity for EHR supporters in the federal government to boost adoption nationwide. A major section of the ARRA entitled Health Information Technology for Economic and Clinical Health (HITECH),32 put billions of dollars in federal incentives into play to spur the adoption and “meaningful use” of EHRs. There was only one catch—providers had to move quickly to secure the funding.117 HITECH had a dramatic effect: Over the next few years, roughly 55 percent of eligible physicians and nearly 4,000 hospitals took advantage of HITECH’s incentives. To date, about $5.9 billion in incentive payments has been disbursed to doctors, and $8.7 billion has been provided to hospitals.33

Not surprisingly, federal engagement in promoting EHR development drew in private firms and investors. Between 2007 and 2012, the EHR market doubled from $9.5 billion to $20.7 billion in annual activity.19 As a result, health care institutions and providers found themselves with an abundance of options.

Despite the surge in public and private investment, EHR adoption in the United States continues to lag adoption in other high-income countries.21 Today, about 80 percent of U.S. hospitals have a basic EHR system,22 but less than 50 percent meet “meaningful use” criteria.23 Approximately half of health care professionals use some sort of EHR,22 but only 10 percent of physician offices meet meaningful use criteria.24

Multiple Barriers to Adoption
Rapid adoption of EHRs has been hindered by a variety of factors, including a fragmented marketplace, changing federal incentives, provider uncertainty about the regulatory landscape, and the striking lack of interoperability between systems. Uptake has been particularly slow among smaller hospitals and physician groups. Notwithstanding the availability of federal subsidies, cost remains a concern for many health care providers.25 Many perceive that the eco-
nomic benefits of installing an EHR system largely accrue to payers and vendors (through efficiencies in diagnostic testing and use of medications); however, health care providers must bear the cost of implementation.25 Although federal incentive payments have helped defray startup costs, much of the money invested to date has gone to large hospitals and multispecialty physician practices, largely to replace or upgrade previously acquired platforms. Smaller hospitals, rural facilities, and small physician practices continue to hold back.26–28

A major factor in predicting whether or not a small- to medium-sized practice will adopt an EHR is physician “technology readiness”—their perception that they are themselves sophisticated technology consumers and their belief that the technology is easy to use, is useful, and gives the practice a comparative advantage.29 Many physicians fear that installing an EHR will disrupt clinic workflow, generate high maintenance costs, and, if the system proves difficult to use, slow them down. Lack of interoperability is a problem,25, 30, 31 as are concerns about assuring data security and patient privacy.25, 30, 31

**HITECH Promotes Adoption of Existing Systems, Not Better Ones**

The incentive payments offered through the HITECH act undoubtedly accelerated adoption of EHRs, but physician practices and medical centers had to move too quickly to qualify for incentive payments. Even the national coordinator for health IT at the time, Farzad Mostashari, referred to the “rush” for adoption.34 If the EHRs that these hospitals and practices purchased were not ideally configured to meet their needs, they could ultimately delay the adoption of more functional health information technology.35

One feature that many current systems lack is interoperability. HITECH’s language clearly indicated that Congress wanted HIT systems to be interconnected and interoperable so that they can readily share data between providers. For this reason, HITECH specified that to qualify for “meaningful use” incentive payments, providers must not only use their EHR in a meaningful manner, but also demonstrate that it is “connected” in a way the provides for the electronic exchange of health information.36

Unfortunately, the rules that the U.S. Department of Health and Human Services (HHS) issued to guide implementation of HITECH watered down the requirement for connectivity. The practical effect was to promote adoption of existing platforms, rather than encourage the development of interconnected systems.

Although this decision was welcomed by large vendors and many health care systems, it was criticized by others. In a subsequent hearing before the House Ways and Means Subcommittee on Health, a national health IT expert offered the following observations:

Unfortunately, the [interoperability] measure specified for 2011 and 2012 is to “perform at least one test of the EHR’s capacity to electronically exchange information.” There is no requirement to implement authentication, consent, authorization, disclosure management, or any other services specifically mentioned in the HITECH Act that are essential to genuinely enable secure electronic exchange of information. Moreover, the test can be performed with “dummy” data for a “fictional patient.”

My view is that this is not really exchange, and comes nowhere close to what was intended by Congress when it passed HITECH. It’s not good enough . . . . By eliminating any real requirement for HIE [health information exchange] until 2013, the final meaningful use rule dramatically undermines the incentives to innovate and invest in the infrastructure necessary to enable it.37
At the same hearing, David Blumenthal, M.D., who was the national coordinator for health IT at the time, was pressed to explain why HHS was not taking more forceful action to promote interoperability. He offered an unusually candid response:

> You need the ‘pipes’ to enable information to flow, and you need agreements among doctors and hospitals about the terms of the exchange. . . . You also need to verify who’s a doctor and who’s not; you don’t want information flowing to people who don’t deserve to have it. . . . We have a system in which there’s virtually no information exchange going on at all. We’re doing a lot of things to make exchange easier, such as setting standards for interoperability . . . . We are moving toward robust exchange, but we are starting where we think industry is, and putting them on notice that they are going to have to move fairly rapidly while we help them along.\(^{118}\)

By subsidizing “where the industry is” rather than where it needed to go, HHS rule-makers allowed hospitals and health care providers to use billions in federal subsidies to purchase EHRs that did not have the level of connectivity envisioned by the authors of the HITECH act.\(^{36}\) The result was far short of the “interoperable and interconnected” network that the RAND team envisioned in its 2005 analysis of the benefits of EHRs.\(^{61, 35}\)

**Cost and Health Impact**

Widespread adoption of interoperable and interconnected EHRs could bring substantial benefits to American health care and the U.S. economy.\(^{19, 38}\) Unfortunately, most of the systems in place today do not “talk” to each other. In addition, few health care systems have redesigned their work processes to take advantage of the functionality that HIT offers.\(^{39}\) This has blunted the benefit that EHRs are supposed to provide.\(^{35}\)

**Clinical Impact of EHRs**

The potential of EHRs to improve patient care is a major factor driving the push for adoption. It is thought that widespread use of EHRs could reduce medical errors by decreasing errors in communication, inaccurate dosing, and missed drug–drug interactions.\(^{40–42}\) EHRs could also improve care by issuing patient and provider reminders for prophylactic care, ensuring adherence to clinical guidelines by providing point-of-care decision support, disease surveillance, and patient monitoring.\(^{43–45}\) Despite these theoretical benefits, studies of the impact of EHRs on the processes and outcomes of care have generated mixed results.\(^{46–52, 53}\)

In 2010, DesRoches and colleagues examined EHR adoption in U.S. hospitals and its relationship to quality and efficiency. Across the large number of metrics they examined, they found that the relationships were “modest at best and generally lacked statistical or clinical significance.” Although the authors noted that use of clinical decision support produced small quality gains, they concluded that simply promoting widespread adoption of EHRs is unlikely to have a major impact on quality. Instead, they concluded that “policies are needed that encourage the use of electronic health records in ways that will lead to improvements in care.”\(^{119}\)
Economic Impact
EHRs’ principal economic impact to date has been facilitating clinical documentation to support timely and complete billing. EHRs can also be programmed to generate reminders and prompts to boost follow-up visits and routine health care. The data on the impact of EHRs on health care operations are less clear. Some organizations have reported improved performance, but others have reported less-favorable findings.

Viewed in hindsight, it is not surprising that introducing IT to health care did not immediately generate substantial gains in productivity. Other industries that adopted IT much earlier experienced similar growing pains. In the 1970s and 1980s, a time when the computing capacity of the U.S. economy grew more than a hundredfold, productivity growth fell to less than half the average rate over the preceding 25 years. The affected industries responded by modifying their IT systems to make them easier to use and by revising work processes to take advantage of IT’s capabilities. Once that was done, productivity soared. Because health care did not learn from the early adopters of IT, it appears destined to follow the same path.

Societal Benefits of EHRs
Properly designed, EHRs should enable a robust research infrastructure through increased depth and breadth of accessible stored data and enabling real-time data analysis. Population health could be improved by increasing vaccination rates and by enhancing the ability of health care providers to swiftly spot emerging public health threats. Although such benefits could generate substantial cost savings for the health care system and society as a whole, they are largely based on modeling and optimistic projections of EHR uptake and performance.

Barriers to Success
The theoretical case for EHRs is strong, but the technology’s promised impact is currently blunted by limitations in its design, uptake, and use.

Lack of Interoperability
The health IT systems that currently dominate the market are not designed to talk to each other. This problem might have been avoided if the federal government had pressed the issue when meaningful use standards were being drafted. Instead, interoperability standards were watered down, and vendors were allowed to apply for meaningful use certification post-market. It is unclear how many, if any, were rejected.

The practical effect of the HITECH Act was to shift the government’s early focus from encouraging interoperability to accelerating uptake of existing EHRs, provided they met criteria for “meaningful use.” Although the act called for the creation of health information exchanges, the final rules that the administration issued to guide implementation set a low bar for interoperability. Instead of using federal incentives to spur development and sale of interoperable EHRs, the Office of the National Coordinator for Health IT sought to bring the health care industry on board.

Advocates of interoperability were disappointed. In their view, dropping the requirement for functional health information exchanges eliminated the industry’s incentive to develop interoperability. As one critic noted, this created “a vicious cycle where the lack of incentives breeds lack of investment and innovation, thereby perpetuating the lack of [Health Information Exchange] capabilities.”
The landscape for interoperability should begin to change in 2014, when EHR provisions included in the Affordable Care Act (ACA) take effect. They will raise the bar for physicians and hospitals to qualify for federal incentives in 2014. The new standards will require that future EHRs connect to a health information exchange. Over 700 EHR vendors and thousands of providers must adopt common data standards to enable interoperability.67 The Office of the National Coordinator (ONC) has established specific goals for health information exchange, including policies to facilitate directed exchange, query-based exchange, and consumer-mediated exchange.68

If the ACA’s EHR provisions are not weakened or delayed, the move to greater interoperability should substantially increase the value of EHRs to health care providers and their patients.29, 69–71 The shift will be less welcome to large legacy vendors because it will blur the competitive edge they currently enjoy.72 Health care systems may be less-than-enthusiastic adopters because functional HIEs will make it easier for patient to see nonaffiliated healthcare providers or switch to a competing health care system.35 Irrespective of industry ambivalence, the Office of the National Coordinator for Health IT is determined to press ahead.34

Some communities are attempting to bridge the interoperability gap by creating regional health information exchanges to provide for limited information-sharing between systems. In most cases, this is on a “read-only” basis, but that is far better than nothing. In theory, this capability should be particularly helpful for emergency care because the time-critical nature of patients’ problems may compel them to seek care at a hospital other than at their usual source of care (and therefore, beyond the reach of their EHR). In those cases, in the words of an emergency physician who is an expert in EHRs, “I have to work with family members to assemble a medication list (which is often incomplete), order tests that may have already been done recently, and risk delivering treatments that may have caused previous adverse effects.”121 Recently, a study done in Memphis, Tenn., found that having access to a regional health information exchange reduced repeated emergency department imaging for headache and back pain.122 But the exchange was used only 12.5 percent of the time, in all likelihood because physicians had to use a separate, password-protected portal that required substantial time and effort to access. In another health care system with a more facile portal, emergency department physicians integrated records across different health care systems in 57 percent of encounters.121

Usability matters.

Uncertain Return on Investment

EHRs were supposed to produce major savings through improved efficiency and better clinical outcomes.19 To date, the federal government has invested over $14 billion to secure these benefits. However, much of the literature detailing the promised benefits of EHRs was based on a small number of early EHR adopters, so it may represent “best case” examples.43 Currently, a large gap remains between the postulated and realized benefits of HIT.46

There are three main reasons why the economic benefits of EHRs have been disappointing to date. First, uptake has been slower than predicted because of high acquisition costs and concerns about the cost of ongoing maintenance. Many providers also fear the disruption of office workflow and are not convinced that EHRs will generate long-term savings. Privacy concerns and fear of unintended consequences are limiting uptake as well.38, 54, 73, 74 The combination effects of limited interoperability and slow uptake have limited the “network effects” that fueled the success of the telephone and, more recently, social media sites like Facebook and Twitter.35
Second, lack of usability is an ongoing problem. Many clinicians complain that EHRs hinder their productivity via nonintuitive interfaces and cumbersome search mechanisms. To be maximally efficient, EHRs should be designed to be as easy to use as a consumer IT system (Table 3.1). Some of the helpful features of EHRs can be problematic if they are not properly calibrated. For example, some EHRs generate so many alerts about possible drug–drug interactions that providers tend to disregard them—a practice that increases the risk of medical errors. To address concerns like these, the Agency for Healthcare Research and Quality (AHRQ) commissioned RAND to develop a guide to reducing the unintended consequences of EHRs. It can be downloaded for free.

The third major barrier to ROI is the failure of many health care organizations to redesign workflows, redefine provider roles, empower self-care, and optimize other processes, such as utilization of inpatient beds to increase efficiency and productivity. Once such changes are made, the promised productivity gains of EHRs and other forms of health IT should become increasingly apparent.

### Determining Ownership of Personal Health Information

Efforts to facilitate the exchange of health information between providers must be balanced against the need to assure the patient’s privacy. Some states, such as New Hampshire, have moved proactively to define in statute that patients control their personal health information.

But regardless of who “owns” patient data, current vendor practices make extracting the data difficult. Many vendors include a clause in their service contracts that precludes independent data extraction from their software. Others have complicated the process by requiring multistep information requests for data transfer. Some institutions have responded by exporting their clinical data to third-party sites for management.

EHRs can improve care coordination and patient engagement, but only if information can be exchanged between providers and, ideally, accessed by patients. The federal government’s “Blue Button” initiative is intended to make it easier for patients to access their own health information and share it with different health care providers. Although versions of Blue

### Table 3.1

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<th>Health IT and Consumer IT Comparisons</th>
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<td>Dynamically updated, data-driven personalized recommendations</td>
<td>Rule-based, poorly integrated into user experience</td>
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<td>Innovation cycle</td>
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<td>Development paradigm</td>
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<td>Architecture</td>
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<tr>
<td>Interoperability and collaboration</td>
<td>High degree of cross-platform interoperability – standard integration with mobile and social platforms</td>
<td>Proprietary designs and terminologies not well-suited for interface; poorly integrated information exchange</td>
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NOTE: Table devised by Daniella Meeker of RAND, used with permission.
Button are already available to veterans, uniformed service members, Medicare beneficiaries, and some private insurance company beneficiaries, access to it is not required by law.\textsuperscript{79} Blue Button depends on the content being available in the source data. For this reason, the amount of data that can be accessed by a veteran in the VA health system is different from the amount available to a Medicare beneficiary.

Blue Button is helpful, but it is only one piece of the puzzle. It does not give patients personal control over their electronic health information because it does not allow them to transmit their medical record in a standard, computable format to a health care provider of their choice. The federal government has recently taken preliminary steps to encourage health IT vendors to add functionality that will allow patients to view, download, and transmit their electronic records to a third party. In 2014, view, download, and transmit functionality will be required to qualify for federal incentive payments.\textsuperscript{80} This development is overdue. Although writers have described personal health data as a new “asset class,”\textsuperscript{81} the truth is that few patients currently have the ability to access or manage their own health information. Many patients still come to the ER with a bag of medications, copies of paperwork, or a medical ID bracelet as their only form of health information.\textsuperscript{82}

**Concerns About Patient Safety**

Espoused as a powerful tool to advance patient safety, EHRs have inadvertently spawned new types of medical errors that are inadequately monitored or regulated. In a 2012 report on this subject, the noted that vendor-imposed non-transparency clauses make it difficult to quantify and track EHR-related medical errors. The IOM also noted that safety monitoring is hindered by a lack of consensus regarding EHR quality measures and the absence of an organization with the power to exercise oversight.\textsuperscript{18}

Vendor gag clauses not only limit the ability of researchers, providers, and regulators to access data regarding EHR glitches that may jeopardize patient safety,\textsuperscript{18, 72, 83, 84} but they also discourage providers from participating in surveys regarding usability. Many EHR vendors collect user-generated information about software glitches for their own purposes, but they regard the information as proprietary. Because few vendors share their observations with the U.S. Food and Drug Administration (FDA), the agency lacks the ability to identify problems and recommend (or, if need be, require) solutions.\textsuperscript{72}

In a recent effort to promote self-regulation of the industry, some vendors have joined together to propose an EHR Code of Conduct that drops the clause that hinders patient safety reporting. However, adherence to the code is voluntary.\textsuperscript{83} While the industry ponders how to respond, the number of EHR-related medical errors grows.\textsuperscript{18, 84}

**Two Platforms, Two Approaches: VistA and Epic**

Two of the largest and most successful EHRs in the nation—the Veterans Health Information Systems & Technology Architecture (VistA) and Epic, one of the most successful privately financed EHRs on the market today—provide an interesting study in contrasts. Both systems are based on versions of the same antiquated but powerful programming language (MUMPS), but their differing origins, business models, and trajectories offer useful insights into the development, diffusion, and potential future of EHRs.
**VistA**

The archetype of an enterprise-wide EHR solution, VistA is installed throughout the Veterans Healthcare Administration, the largest integrated delivery system in the United States. Intensively studied since its inception, VistA has received numerous accolades for reducing costs, improving patient care, and enhancing clinical outcomes in the VA health care system.\(^3,85\)

Because its architecture is designed to enable the ready retrieval and analysis of clinical data, it is a powerful tool for quality improvement and health services research.

**Systemwide Benefits Demonstrated**

Developed in its present form in the mid- to late 1990s, VistA was the first EHR to demonstrate the benefits of adopting an enterprise-wide health information system. It also provided users and observers with the first sense of what EHRs can do for the quality and efficiency of care. In 2009, nearly half of hospitals with enterprise-wide (inpatient and outpatient) health IT systems in the United States used VistA or VistA derivatives.\(^86\)

Today, VistA and derivative EHRs, such as the Resource and Patient Management System (RPMS), are installed in every Veterans Health Administration (VHA) facility in the country, as well as in most of the Indian Health Service and a number of private health care facilities.

VistA originated in the Office of Data Management and Telecommunications in the late 1970s, when individual VA medical centers began simultaneous development of computerized solutions for prescription management, patient scheduling, patient registration, patient discharge, and radiology.\(^3\) This prompted VA developers to come together to agree on a common coding language and dictionary, as well as programming standards that allowed design code portability across systems. Known at the time as the Decentralized Hospital Computer Program, this collaborative, nationwide effort was kicked off in 1983. It was implemented in waves consisting of 25–100 sites at a time that adopted select applications.\(^3\)

The pace and scope of EHR adoption increased dramatically under the leadership of Dr. Kenneth W. Kizer, who served as the VA’s Undersecretary for Health from 1994 through 1999. Dr. Kizer considered installation of a major system upgrade to be a core element in his effort to transform the organization and delivery of care throughout the entire VA health care system, along with changing the VA’s payment system, implementing a national performance management system, instituting universal primary care, and other strategies.\(^3,87,88\)

The most significant aspect of the VA’s IT upgrade was the addition of a graphical user interface for health care providers known as the Computerized Patient Record System (CPRS), which served as the “face” of VistA’s EHR. Systemwide implementation of CPRS-VistA began in early 1997.

VistA incorporated, and in some instances pioneered, a number of useful features, including computerized order entry, electronic prescribing, bar code medication administration, and embedded clinical guidelines. With VistA, a VA health care provider could easily review and update a patient’s electronic medical record and share this information with any other health care provider in the VA’s national system.\(^3\)

VHA-wide implementation of VistA took place between February 1997 and December 1999. It was (and remains) the largest and most rapid deployment of an EHR ever done.\(^88\)

**VistA Credited with Improving Veterans’ Health**\(^88\)

The positive impact of VistA has been documented in outpatient chronic disease management;\(^89\) in the VA’s systemwide Quality Enhancement Research Initiative (QUERI) processes;\(^90,91\) and in overall assessments of performance indicators of preventive, outpatient, and
The open-source design of the system encouraged innovation without sacrificing interoperability. For example, the VA's Cardiovascular Assessment, Reporting, and Tracking System for Cath Labs system for supporting cardiac catheterizations in the VA system improved quality and safety while simultaneously creating a large data repository for research.

The product of an $8.5 billion federal investment over roughly 30 years, VistA was part of a broad reorientation and redesign of the VHA. The bet paid off. Between 1996 and 2004, the VHA accommodated nearly 70 percent more patients, lowered its employee-to-patient ratio by 37 percent, and decreased its overall costs per patient at a time when Medicare and private insurance costs were dramatically rising. VistA was praised for helping the VHA improve patient care, boost efficiency, lower costs, and strengthen its quality improvement and research infrastructure.

VistA's success has been attributed in large part to the collaborative nature of its development. Clinicians and IT experts worked together to design its user interfaces and patient record system. Equally if not more important, because VistA is built on a standard code and maintains data-sharing capability between sites, it is fully interoperable within the VA.

Independent surveys suggest that physicians are broadly satisfied with VistA compared with other EHR systems. In a 2011 survey by the American Academy of Family Physicians (AAFP) and a similar 2012 poll by Medscape, VistA outscored the large majority of health IT solutions, particularly those offered by large vendors like Epic and McKesson. When the AAFP survey asked respondents to express their level of agreement with the statement, “This EHR enables me to practice higher quality medicine than I could with paper charts,” VistA received the top score. In both the AAFP and Medscape survey’s, VistA was one of the highest-ranking systems overall.

**OpenVista**

In 2002, two venture capital–supported entrepreneurs, with guidance from Dr. Kizer, founded Medsphere Systems Corporation. Their goal was to market OpenVista, a version of VistA adapted for commercial use, in the private sector. The company continues to spend millions annually to refine this system to meet the needs of nonfederal hospitals.

Some prospective users of OpenVista have expressed concern about its antiquated coding language (interestingly, the same basic coding language used by Epic), potential maintenance costs, and warnings from competing vendors that the platform was not designed from the ground up to support fee-for-service billing. A 2005 effort by CMS to offer a free version of VistA to support private doctors' offices was unsuccessful.

Despite these obstacles, the usability, affordability, and documented impact of VistA have enabled Medsphere to gain a foothold in the private health care sector. Currently, more than 25 private hospitals use OpenVista, including large urban teaching facilities, such as Lutheran Medical Center in Brooklyn. OpenVista is deployed in a wide variety of facilities, including an 11-bed Guadalupe County Hospital in New Mexico, the Silver Hill psychiatric hospital in Connecticut, and the nine hospitals that comprise the West Virginia state hospital system. Medsphere also developed and supports the Resource and Patient Management System (RPMS), a derivative of VistA. It is currently deployed in more than 370 clinical sites of the federal Indian Health Service.
Cost Is a Major Differentiator Between OpenVista and Other Private EHRs

According to Medsphere, no hospital has spent more than $3.5 million over a five-year period on OpenVista implementation and ongoing maintenance. All of Medsphere’s clients who are eligible for federal incentives have achieved Stage 1 of meaningful use, and almost all will cover their initial five-year costs for installing OpenVista through their incentive payments.

Epic

Epic is rapidly becoming an industry leader in the EHR marketplace, particularly among large academic medical centers and multispecialty group practices. A privately held company, it develops, installs, supports, and owns its proprietary technology. Among its 260-plus clients are most of the United States’ elite academic medical centers, including the Cleveland Clinic, Johns Hopkins, Dartmouth-Hitchcock Medical Center, Kaiser Permanente, and nearly the entire University of California system. Epic has won several awards for both inpatient and outpatient EHRs, as well as for software used in scheduling, billing, and collections. It has been named “The Top EHR Vendor by Number of Meaningful Use Attestations.”

Started in 1979 as a small company of 1.5 employees called Human Services Computing, Inc., Epic has been led from the beginning by its founding CEO, Judith Faulkner. Over the subsequent decades, Faulkner turned an initial investment of $70,000 in private funds into a global company with approximately $1.5 billion in revenue in 2012. Epic’s breakout moment came in 2003, when Kaiser Permanente chose it over two much larger companies—IBM and Cerner—to provide the EHR for its 36 hospitals and 8+ million members. According to a former VA official, Kaiser’s leadership also considered VistA, but soon abandoned the idea because there was no commercial vendor at the time to support implementation and maintenance.

In contrast to many startup companies, Faulkner built Epic without relying on outside capital and with almost no marketing. Because it has remained a privately held company, it does not disclose its earnings. But industry analysts note that it is clearly profitable and has zero debt. Much of Epic’s growth comes through word-of-mouth advertising built on a client base of elite academic institutions. The formula has worked brilliantly. According to a recent article in Forbes magazine, “By next year [2013], 127 million patients or nearly 40% of the U.S. population will have its medical information stored in an Epic digital record.” In Medscape’s 2012 survey of EHRs, Epic was the most-used system by a wide margin.

Closed Platform Makes Interfacing Epic Challenging

In contrast to VistA, which is in the public domain, Epic is a closed platform. It can be challenging and costly for hospitals to interface their EHR with the clinical or billing software of other companies. Forbes observed, “In addition to the software, [Epic] customers pay dearly for hardware, and for the army of Epic-certified technicians that needs to be deployed to get the system up and running.” Although Epic is expensive, it works, and in the conservative world of health IT, that’s all that matters. Another Forbes article put it this way: “Epic is built on a traditional client server model, and does individual, customized installations for each client; a reputation for near-flawless implementation—derived by tightly constraining how much idiosyncrasy is engineered in each install—has been a prime driver of growth.”

Given its strong market position, Epic was well positioned to compete for new contracts when the HITECH Act of 2009 put billions of dollars in federal incentive payments into play. As the only head of a health IT company appointed to serve on the Obama administration’s
Federal Health IT Policy Committee, Faulkner was able to advise the national coordinator for health IT and other federal officials as they crafted a policy framework to develop a nationwide health information infrastructure, including the criteria that HHS ultimately adopted to satisfy HITECH’s requirement that IT platforms be able to exchange health information.98, 102

Today, Epic is a market leader in helping users of its system meet meaningful use criteria.96 Several studies have described various ways in which Epic contributes to improvements in care. Examples include enabling providers to identify high-risk patients prior to performing interventions, thereby reducing nosocomial infections,103 and use antibiotics more appropriately.104 In a randomized controlled trial of Epic in primary care sites, Epic’s Best Practice and SmartSet platforms were able to decrease prescribing of heavily marketed pharmaceuticals and lead to more–cost–effective care.105 Epic has been credited with playing an important role in quality improvement efforts in the Kaiser Permanente system, including use of best practice alerts, standardized order sets, and chart abstraction tools.106 Epic has been shown to decrease redundancy of testing and utilization.107, 108

However, not all evaluations of Epic’s impact have been positive.43, 47, 104–107, 109–112 An independent evaluation of Epic’s impact in the Kaiser system found that implementation led to efficiency losses and a persistent two-minute increase in the length of time of an average patient encounter.111 Implementation of Epic in the Hennepin Health system did not change outcomes for critically ill patients. Moreover, physicians complained of workflow interruptions, slower processes of care, and excessive time with the provider’s “back to the patient” because of the need to focus on computerized order entry.47

**Epic’s Limited Interoperability Is a Major Concern**

One of the biggest concerns with Epic is its relative lack of interoperability.100 Although the company has a strict structure and retains tight control of its software and data, it does customized installations for each client. This allows health care systems to tailor Epic’s applications and functionality to meet their own needs. Customizability is attractive to hospital CEOs, CFOs, and some members of the medical staff, but it can limit interoperability between sites and the capacity to communicate with providers who use other EHRs.

While there is potential for EHRs with functional data linkages to be used for research purposes, currently the lack of interoperability between EHRs hinders research capabilities.113 Furthermore, many EHR fields contain free text, which makes subsequent extraction and analysis difficult.114 To circumvent these limitations, the Cleveland Clinic Neurologic Institute developed a distinct program that is incorporated into the patient’s workflow in order to facilitate data collection for research.114

To address concerns about lack of interoperability, Epic developed Care Everywhere. The feature allows Epic users to communicate with other health systems’ EHRs, although it works best if both parties have Epic systems. According to the company’s website,

Care Everywhere provides a framework for interoperability, so that wherever the patient goes—between healthcare systems in the same town or across state and national borders—the clinicians providing care can have the information they need. Information can come from another Epic system, a non-Epic EMR that complies with industry standards, or directly from the patient. When an Epic system is on both sides of the exchange, a richer data set is exchanged and additional connectivity options, such as cross-organization referral management, are available. Regardless of the information source, Care Everywhere connects it to your EpicCare EMR, giving clinicians a more complete clinical record.128
Epic’s hold on America’s top hospitals is powerful and increasingly pervasive. Numerous theories for Epic’s dominance abound, but its market share among leading academic medical centers is undeniable. It is less clear what clients are getting in return. Last year, a writer for *Forbes* offered the following observations:

She [Judy Faulkner, Epic CEO] has quietly convinced them [hospital chief information officers] that her product is best: a single, seamless database—the fruit of a company that has grown organically, and shunned acquisitions. And, because it is no small task to deploy, she is there all the way to hand-hold jittery CIOs, and help them get millions of dollars in government subsidies by showing meaningful use of her EHR. Her not-for-profit clientèle will need every penny of those taxpayers’ dollars, but they won’t cover anywhere near the staggering cost of an Epic EHR. Duke University Health System will shell out $700 million, so will Boston-based Partners HealthCare; University of California, San Francisco will pay $150 million.

It is impossible to independently verify the accuracy of the sums quoted in the Forbes article. Health IT experts contend that a health care system should devote 3–4 percent of its annual budget to IT. Given the annual revenues of some of these systems, the reported levels of spending in the Forbes article are more or less in line with that figure. However, it should also be noted that capital expense is only part of an EHR’s cost. Many hospital administrators fail to consider the additional spending required to train (and retrain) personnel, the downtime involved in learning a new system, the costs of maintenance and the inevitable upgrades, and other hidden costs. As a result, it is difficult to determine the true costs of IT adoption from public data.

**The EHR “Productivity Paradox”**

David Brailer, the first national coordinator for health information technology at HHS, once described VistA as “probably one of the most stress-tested, and life-tested electronic health records in the world.” It is an ongoing success story in the VA health care system. However, despite its relative ease of use, interoperability, and impact, VistA’s private-sector counterpart, OpenVista, has experienced limited success.

While OpenVista has had relatively few takers, Epic has established itself as the enterprise-wide solution of choice for large private health care systems and academic medical centers, irrespective of ongoing concerns about its limited interoperability and less-than-ideal usability. As a result, Epic has been able to capitalize on the recent surge in federal incentive payments to encourage doctors and health care systems to adopt or upgrade their EHR to meet the government’s meaningful use standards.

If health care systems continue the current trend of consolidating into large integrated delivery systems, and the small hospitals and physician practices that have been sitting on the fence get drawn in, Epic could become the dominant vendor of EHRs in the United States. Two technology writers recently envisioned a day when “Epic will be health IT’s (HIT’s) Roman Empire: establishing the laws and the language for “known world”, as well as the underlying infrastructure, and ends up shaping information flows, IT architecture and—potentially—the eventual configuration of provider systems.”
Alternatively, American healthcare will adapt to health IT’s “productivity paradox” the way financial services, airlines, and other industries did before it.\textsuperscript{39} The same pair of technology writers described what might happen next:

The second group of scenarios—we call them “Open Data”—assume that progress on interoperability standards, together with Epic’s focus on convincing large clients to adopt its functional but hardly delightful software, will create an opportunity for an agile competitor to compete effectively for the long tail customers, especially those who’ve deliberately avoided participation in a large hospital system, and might especially value an EMR system that offers a great user experience, and doesn’t distance the physician from the patient the way most [EHRs] tend to do.\textsuperscript{101}

There are signals that pressure is growing on EHR vendors to make their systems more interoperable, usable, and patient-centered. Recently, several of Epic’s top competitors, including McKesson and Cerner, signed an agreement that they will work together to improve interoperability between their systems.\textsuperscript{108} It is too early to know what will happen next, but two things are clear: (1) EHRs are here to stay; and (2) how they are designed and employed will profoundly influence the quality, efficiency, and cost of American health care for decades to come.

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Case Study 4

Haemophilus influenzae Type b (Hib) Vaccine

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The Technology

Haemophilus influenzae type b (Hib) vaccine is a childhood vaccine that protects against Hib infection, a bacterial disease that was a major cause of death and disability in young children. The vaccine is composed of the capsular polysaccharide of the Hib bacterium chemically bound to a carrier protein. When injected, the vaccine elicits a protective antibody response, even in infants with immature immune systems. Protection is lifelong.

Rationale

In a third of a century, the development, adoption, and widespread use of Hib vaccine has dramatically reduced the incidence of Hib infection in the United States and subsequently in many other parts of the world. Before the 1970s, Hib disease affected one in 200 children in the United States under the age of 5 years.1 Even after the advent of antibiotic treatment, 5 percent of American children who contracted systemic Hib disease died.2 Hib was the most common cause of childhood meningitis; it also caused several other serious diseases, including septicemia, epiglottitis, pneumonia, septic arthritis, osteomyelitis, and cellulitis. In the pre-vaccine era, one in 2,000 U.S. children under the age of 5 years contracted Hib meningitis. Rates of Hib meningitis among African Americans were four times higher than among whites, and among Native Americans, the rates were ten times higher than among whites.3–5 Approximately 30 percent of those who survived Hib meningitis suffered severe neurological sequelae, including mental retardation, deafness, and seizures.6, 7 In fact, for many years, Hib was the leading cause of acquired mental retardation in the United States.6

Meningitis was the most common manifestation of Hib disease, followed by epiglottitis. In developing countries, Hib pneumonia is more common than meningitis.8 Compared with children in developed nations, those in the developing world have higher incidences of Hib infection at younger ages. They also experience far higher rates of mortality (20–40 percent in sub-Saharan Africa).9 In these regions, 30–60 percent of children who contract Hib meningitis die.10–12 It was estimated that in the pre-Hib vaccine era, nearly half a million cases of systemic Hib disease occurred each year worldwide, with an average mortality rate of 23 percent.13 And 30–50 percent suffered lifelong morbidity, mostly due to central nervous system complications of meningitis.13, 14 Recently, scientists have pointed out that seemingly “cured” meningi-
tis patients, including those who are successfully treated for Hib meningitis, suffer slight but important lifelong disabilities. The Hib vaccine changed this grim picture.

Early Adoption

Foundational discoveries stretching back to the 19th century enabled the development of prototype Hib vaccines in the 1970s. In 1892, Pfeiffer described *Haemophilus influenzae* as a Gram-negative bacterium. Forty years later, Pittman classified strains of *Haemophilus influenzae* into two groups: those with capsules and those without (non-typable). There are six capsular types, distinguished by their polysaccharide structures.

Beyond establishing a common language, this classification system has clinical relevance; pathogenicity and protection are type-specific. Those with invasive *Haemophilus influenzae* infection were infected with type b at least 95 percent of the time. Type b is so much worse than the others because, unlike the other capsular types, the type b polysaccharide “shields” the bacterium from the lytic activity of serum complement alone (innate immunity). Consequently, type-specific antibodies (acquired immunity) must be present to initiate complement killing of Hib bacteria.

Infants Are Most Vulnerable to Hib Disease

As the molecular basis for Hib disease became clearer, scientists solved the mystery of why the organism preferentially attacks infants and young children. Antibodies capable of killing Hib are not present in this age group. Newborns have maternally derived protective antibodies, but their levels decline during the first few months of life. Once these antibodies clear a newborn's system, the child is susceptible to infection. This explained why, in the United States, unvaccinated 6- to 24-month-old infants sustain the highest rates of Hib disease. By 6 years of age, most unvaccinated children develop Hib antibodies, either by surviving Hib infection or, mostly, through repeated contact with nonpathogenic microorganisms that carry cross-reactive polysaccharides similar to the Hib capsular polysaccharide.

To protect vulnerable infants, researchers needed to create a vaccine capable of inducing protective levels of antibody to the Hib capsular polysaccharide at a very young age. Because of the immaturity of an infant's immune system, this proved to be a daunting task.

The high incidence and severity of Hib disease led to vaccine development in the 1960s. The work was initiated by two groups of researchers, one at the Albert Einstein College of Medicine and then at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA), and one at Children's Hospital Medical Center, Boston, Massachusetts. Both were supported by the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH). The Centers for Disease Control and Prevention (CDC) provided surveillance, and the FDA reviewed the data, approved clinical studies of the candidate vaccines, and finally licensed them to be marketed to the public.

Two intramural NIH researchers, John B. Robbins and Rachel Schneerson—both employees of NICHD—identified the Hib capsular polysaccharide as an essential virulence factor and a protective antigen as shown previously by Heidelberger for pneumococci; their work aimed to provide a vaccine based on this polysaccharide. In 1969, Robbins and Schneerson initiated a series of studies that ultimately led to the development of the first Hib capsu-
lar polysaccharide vaccine. Their NIAID-supported colleagues, Porter Anderson and David Smith, independently developed a Hib polysaccharide vaccine at the Children’s Hospital of Boston during the same time. The two groups then conducted clinical studies of the Hib polysaccharide vaccine.

In order to study the Hib vaccine in humans, scientists needed to first quantify the normal amount of Hib antibody in humans. Robbins and Schneerson measured the amount of Hib polysaccharide antibody in a volunteer who received the vaccine. This allowed other scientists throughout the world to compare Hib antibody levels to the reference level. Robbins and Schneerson went on to study Hib antibody levels in patients with an immune deficiency disorder called X-linked hypo-gammaglobulinemia. Preparations of the full complement of human antibodies were routinely injected to protect these patients from infections like Hib. Because they knew the amount of Hib antibody in each injection, Robbins and Schneerson were able to determine the amount of Hib antibody that afforded protected from Hib infection. A Finnish study confirmed their estimate, and the scientists agreed to use this protective threshold for assessing vaccines.

Now scientists could match protective levels of Hib antibody to efficacy in preventing disease in large numbers of individuals. Two controlled, randomized efficacy studies were conducted in 1974: in Mecklenburg County, North Carolina, involving 16,000 children, and in Finland, where nearly 100,000 children were immunized. Both studies confirmed safety, few side effects, and sufficiently protective levels of antibody in children two to five years old. However, both studies also showed low antibody levels and insufficient protection against Hib in children less than 18 months old. The Finnish study demonstrated vaccine efficacy of 90 percent at one year in children older than 18 months (95-percent confidence interval, 56 to 96 percent).

While this work was being done, Anderson and Smith advanced science on the Hib polysaccharide vaccine. They translated their scientific work into a commercial pharmaceutical company, Praxis Biologics, in 1983. As a result of the efforts of this team, Robbins and Schneerson's work, and the contributions of others, three nearly identical polysaccharide vaccines against Hib were licensed in 1985: b-Capsa® by Praxis Biologics, HibVAX® by Connaught Laboratories, and Hib-Immune® by Lederle Laboratories.

Initial Use

These First-Generation Vaccines Represented a Major Advance But Had Important Limitations

The new Hib vaccines induced protective levels of Hib antibodies in older children and adults and prevented systemic Hib disease without significant adverse reactions. However, they failed to stimulate protective Hib antibody levels in children younger than 18 months old. This was a serious shortcoming, because this is the age group with the highest risk of contracting life-threatening Hib disease. Around this time, researchers determined that crowded conditions are an important risk factor for transmitting Hib disease, because the infection spreads by droplets from one child to another. This was a particular concern at day care centers.

Despite these shortcomings, the first-generation Hib vaccines represented a major breakthrough in science. They prevented life-threatening disease in the 25 percent of cases that occur after the first two years of life. Although the basis for licensing Hib vaccine for children
24–59 months of age was largely supported by the 1974 Finnish and Mecklenburg County studies, which showed protective effects at two years of age. The CDC’s Advisory Committee on Immunization Practices (ACIP) recommended administering the vaccine to children as young as 18 months if the child attended day care or was otherwise high-risk.

### Expansion of Use

#### Initial Studies Produce Mixed Results

Following the licensure and adoption of first-generation Hib polysaccharide vaccines, placebo-controlled trials were no longer ethical. To evaluate the efficacy of these vaccines among U.S. children younger than five years of age, five case-control studies were performed. Two were supported by the CDC: One sampled day care attendees (vaccine efficacy 41 percent with a statistically nonsignificant 95-percent confidence interval of –6 to 68 percent); the other sampled young children without day care attendance (vaccine efficacy 62 percent with 95-percent confidence interval of 7 to 84 percent). The third study evaluated members of the Northern California Kaiser-Permanente Health Plan (vaccine efficacy 69 percent with statistically nonsignificant 95-percent confidence interval of –13 to 91 percent). The final two studies were originally a single study but were later divided into two groups: the Connecticut, Pittsburgh, and Dallas sites (vaccine efficacy 88 percent with 95-percent confidence interval of 74 to 96 percent) and the Minnesota site (vaccine efficacy –69 percent with statistically nonsignificant 95-percent confidence interval –285 to 26 percent).

Based on these unpublished mixed results, concerns arose that the first-generation Hib vaccines were not uniformly effective in different populations. Therefore, in 1987, the American Academy of Pediatrics (AAP) Committee on Infectious Diseases advised no further use of the Hib polysaccharide vaccine in areas that had failed efficacy studies, such as Minnesota. Despite its limitations, use of the first-generation vaccine was recommended.

There were population differences in response, but the FDA and the Advisory Committee on Immunization Practices recommended continued use of Hib vaccine throughout the United States. Later case-control studies revised the record to five studies with positive estimates of Hib polysaccharide vaccine efficacy (41 to 88 percent) and three with insignificant or negative findings. These data are presented in Table 4.1.

More than 10 million doses of first-generation Hib polysaccharide vaccine were administered in the United States between 1985 and 1989. At that point, the first-generation vaccines were swiftly supplanted by more effective second-generation Hib vaccines. Ultimately, the first-generation vaccines had a relatively modest effect on the incidence of Hib infection because they were effective in infants. But they set the stage for the remarkable developments that followed.

### Breakthrough: The World’s First Hib Conjugate Vaccine Is Licensed in 1987

The Hib polysaccharide vaccine was better than nothing, but it did not afford protection for the age groups with the highest incidence of infection. Therefore, the researchers in Bethesda and in Boston continued to work, hoping to develop a more effective vaccine. The breakthrough came when Robbins and Schneerson extended earlier work done by Karl Landsteiner, Oswald Avery, and Walther Goebel. Landsteiner had shown that binding a small molecule that
Table 4.1
Selected Efficacy Studies of the Hib Vaccine

<table>
<thead>
<tr>
<th>Hib Vaccine</th>
<th>Study Period</th>
<th>Site</th>
<th>Study Type</th>
<th>N (Control/Total)</th>
<th>Vaccine Schedule</th>
<th>Efficacy (%)</th>
<th>95% Confidence Interval (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP Meda</td>
<td>1974–1976</td>
<td>Finland</td>
<td>Prospective controlled trial</td>
<td>49,295/98,272</td>
<td>3 mo.–5 yr., booster 3 mo. later if 3–17 mo. at first dose</td>
<td>90</td>
<td>56–96</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>1985–1987</td>
<td>Connecticut; Pittsburgh, Pennsylvania; Dallas, Texas</td>
<td>Case control</td>
<td>152/228</td>
<td>–</td>
<td>88</td>
<td>74–96</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>1985–1987</td>
<td>Northern California</td>
<td>Case control</td>
<td>166/201</td>
<td>–</td>
<td>62</td>
<td>–44 to 90</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>1986</td>
<td>Mo., N.J., Okla., Tenn., Wash., Los Angeles</td>
<td>Case control</td>
<td>129/203, no day care</td>
<td>–</td>
<td>70</td>
<td>17–89</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>1986</td>
<td>Mo., N.J., Okla., Tenn., Wash., Los Angeles</td>
<td>Case control</td>
<td>291/417, in day care</td>
<td>–</td>
<td>45</td>
<td>–1 to 70</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>1988–1989</td>
<td>Minnesota</td>
<td>Case control</td>
<td>–</td>
<td>–</td>
<td>–6</td>
<td>–184 to 60</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>1988–1990</td>
<td>Connecticut; Pittsburgh, Pennsylvania</td>
<td>Case control</td>
<td>–</td>
<td>–</td>
<td>82</td>
<td>38–94</td>
<td>75</td>
</tr>
<tr>
<td>PRP-D</td>
<td>1984–1988</td>
<td>Alaska</td>
<td>Prospective controlled trial</td>
<td>1,048/2,102</td>
<td>2, 4, 6 mo.</td>
<td>35</td>
<td>–57 to 73</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>1985–1989</td>
<td>Finland</td>
<td>Prospective controlled trial</td>
<td>56,000/114,000</td>
<td>3, 4, 6, 14–18 mo. (intervention) vs. 24 mo. (controls)</td>
<td>94</td>
<td>83–98</td>
<td>51, 52</td>
</tr>
<tr>
<td></td>
<td>1988–1991</td>
<td>Finland</td>
<td>Prospective controlled trial</td>
<td>60,500 PRP-D 56,500 PRP-CRM/117,000</td>
<td>4, 6, 14–18 mo.</td>
<td>100</td>
<td>88–100</td>
<td>53</td>
</tr>
<tr>
<td>PRP-CRM (HbOC)</td>
<td>1988–1990</td>
<td>Northern California</td>
<td>Prospective controlled trial</td>
<td>30,680/61,080/20,800</td>
<td>2, 4, 6 mo.</td>
<td>100</td>
<td>68–100</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>1988–1991</td>
<td>Finland</td>
<td>Prospective controlled trial</td>
<td>60,500 PRP-D 56,500 PRP-CRM/117,000</td>
<td>4, 6, 14–18 mo.</td>
<td>100</td>
<td>87–100</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>1991–1992</td>
<td>Los Angeles County</td>
<td>Case control</td>
<td>767/872</td>
<td>2, 4, 6 mo.</td>
<td>94</td>
<td>68–99</td>
<td>55</td>
</tr>
</tbody>
</table>
does not provoke an immune response—called a hapten—to a protein could elicit a strong immune response against the hapten. Avery and Goebel had used the technique to elicit an immune response to a pneumococcus polysaccharide hapten by binding it to a carrier protein. Robbins and Schneerson applied the technique to produce a robust immune response to the Hib polysaccharide by binding it to a different carrier protein. Smith and Anderson in Boston did the same thing using a different method of conjugation.43, 44

The result of this research was the development of a new, second-generation “conjugate” Hib vaccine. It was better than the earlier, polysaccharide vaccine in two important ways: First, the new protein-linked vaccine was more highly immunogenic, so it produced protective levels of antibodies.6 Attaching a protein to the polysaccharide converted the immune response from a T-cell–independent process into a T-cell–dependent process, which enables immunologic memory. As a result, when immunized children were subsequently exposed to Hib or received a second dose of Hib vaccine, they responded with a strong booster effect.31, 37 Second, studies showed that the new conjugate Hib vaccine reduced nasopharyngeal carriage of the bacteria. This conferred a degree of “herd immunity” to unvaccinated children because they were less likely to catch Hib disease from an infected child.13, 31 One study documented a Hib carriage rate of zero in vaccinated three-year-olds, compared with a 3.5-percent carriage rate in unvaccinated children of similar age.31 The superiority of the new conjugate Hib vaccines was so obvious that manufacturers withdrew their remaining stock of first-generation vaccines from the market in 1989.45 Thereafter, only conjugate Hib vaccines were sold.

Ultimately, four types of Hib conjugate vaccines were brought to market. All contain the Hib capsular polysaccharide, polyribosylribitol phosphate (PRP), but each links the PRP molecule to a different protein. The first Hib conjugate vaccine to reach the market was the diphtheria toxoid conjugate (PRP-D) created by Robbins and Schneerson. It was later modi-
fied and produced by Connaught Laboratories as ProHIBiT.® In 1987, the FDA licensed PRP-D for children 18 to 60 months old.® Next came the mutant diphtheria toxin conjugate (PRP-CRM), which was approved for children 18 months and older in 1988 and subsequently approved for use in infants in 1990.6, 42 This vaccine was developed by Anderson with production by Praxis Laboratories and distributed by Lederle Laboratories as HbOC (HibTITER®).® The third vaccine, a meningococcal outer membrane protein conjugate (PRP-OMP; Pedvax-HIB®), uses a protein component developed by Merck Sharp and Dohme.® It was licensed in 1989 for 15- to 18-month-olds and approved for use in infants in 1990.5, 42 With three vaccines on the market, in April 1990, ACIP recommended immunization of children 15 months and older with one of the first three conjugate vaccines. Later that same year, both ACIP and the American Academy of Pediatrics recommended infant immunization with either PRP-CRM (HbOC) or PRP-OMP. By 1991, ACIP recommended initiation of the primary series of Hib vaccine at 2 months and a booster dose at 12 to 15 months.46

The fourth variety of Hib conjugate vaccine to reach the market, a tetanus toxoid conjugate (PRP-T), was developed by Schneerson and Robbins and licensed in 1993. It is manufactured by Sanofi Pasteur as ActHIB.® At various points, it has been marketed under the brand names ActHIB® and OmniHIB®. Another version of PRP-T, HIBERIX® produced by GlaxoSmithKline, was licensed in 2009 for infants and older children.13, 47

Currently Available Hib Vaccines

Today, PRP-T and PRP-OMP are the only Hib conjugate vaccines currently available in the United States.48 PRP-D (ProHIBiT®) was discontinued in 2000, and PRP-CRM (HbOC; HibTITER®) was phased out in 2007. HibTITER® combined with diphtheria and tetanus toxoids and a whole-cell pertussis vaccine (DTP) was marketed for a time as TETRAMUNE® by Lederle-Praxis Biologicals, but it is no longer available. Aventis Pasteur marketed a combination vaccine called TriHIBit (ActHIB® combined with a diphtheria and tetanus toxoids and acellular pertussis vaccine [Tripedia®]) from 1996 to 2011.45 It was used only as the fourth dose in a Hib vaccination series.

The vaccines on the market today are produced in both single-agent and combination forms by Sanofi Pasteur (PRP-T; ActHIB® and Pentacel®), GlaxoSmithKline (PRP-T; HIBERIX® and Menhibrix®), and Merck (PRP-OMP; PedvaxHIB® and Comvax®).48 One PRP-T vaccine, OmniHIB®, by SmithKline Beecham (now GlaxoSmithKline) is no longer available.45 Details regarding current Hib conjugate vaccines are summarized in Table 4.2.

Cost and Health Impact

Hib Vaccines Have Proven to Be Highly Effective in Developed World

All but one of the four versions of Hib conjugate vaccine work well in infants. PRP-D was the exception: It did not perform as well in certain high-risk groups. In particular, PRP-D did not demonstrate optimal efficacy in a sample of Alaskan Eskimo children (N=2102) with a high burden of Hib disease.49 This observation was important because the incidence of Hib disease in 0- to 12-month-old infants was particularly common among Native Americans. In fact, three-fourths of all cases of Hib disease in Native Americans occurred during infancy, compared with roughly half of black and white children.18 Eventually it was determined that of the
four conjugate vaccines, PRP-D produced the smallest antibody response among infants—the group with the highest disease prevalence.50

In a much larger trial conducted in Finland (N=114,000), a nation where Hib disease is less frequent, PRP-D had an efficacy of 94 percent (95-percent confidence interval of 83 to 98 percent) in children older than 12 months.51, 52 A follow-up Finnish trial comparing PRP-D to PRP-CRM found efficacies of 100 percent for both (95-percent confidence intervals of 88 to 100 percent and 87 to 100 percent, respectively).53 The alternate PRP-CRM conjugate vaccine was also found to have efficacy rates of 100 percent (95-percent confidence interval of 68 to 100 percent) and 93 percent (95-percent confidence interval of 70 to 99 percent) in studies conducted in Northern54 and Southern55 California, respectively.
Much like Alaskan Eskimo children did in the late 1980s, Navajo children experienced high rates of Hib disease. The PRP-OMP conjugate vaccine was tested in a sample of Navajo children under the age of 18 months of age and was determined to have an efficacy of 93 percent (95-percent confidence interval of 53 to 98 percent). In this study, rather than administer the usual three doses of the primary series, injections were given at two and four months only to improve compliance. Importantly, substantial protection against Hib disease was documented after the first dose.

Another innovative regimen was used in a United Kingdom trial of PRP-T. This was the first randomized double-blind efficacy study of PRP-T. In this study, three doses were administered on an accelerated schedule at two, three, and four months of age without a subsequent booster injection in the second year of life—the common practice at the time. The outcome of interest was development of invasive Hib disease. Based on “intention to treat” analysis, vaccine efficacy was 95 percent (95-percent confidence interval of 74 to 100 percent) after three doses (85 percent [95-percent confidence interval of 49 to 97 percent]). This means that researchers included all children who were randomly assigned to this treatment group, whether or not they got all three doses of the PRP-T vaccine.

Hib Conjugate Vaccines Are Also Effective in Developing Countries, But Their High Cost and Complex Administration Schedule Limits Their Reach

Research done in developing countries has shown that Hib conjugate vaccines are highly effective in these settings as well. The problem in low-income countries is not vaccine activity but cost. Compared with some other childhood vaccines, Hib is relatively expensive and requires a more complex, multi-dose vaccination schedule to confer a high level of protection. As a result, many low-income countries have concluded that they cannot afford it. This is unfortunate, because the vaccine could make a big impact if it was widely administered in these countries.

To determine the impact of Hib vaccination, the Chilean government conducted its own efficacy studies in Santiago. Subsequent research with a Hib conjugate vaccine demonstrated efficacy of 91.7 percent and effectiveness of 90.2 percent to prevent invasive Hib disease, 91.3 percent to prevent meningitis, and 80 percent to prevent bacteremic pneumonia. Similar findings were reported in Gambia, which was able to use these data to secure outside support for integrating Hib conjugate vaccine into its national immunization program. Later studies in Chile demonstrated that the conjugate Hib vaccine also prevented many cases of Hib pneumonia. This is important, because Hib pneumonia is a bigger problem in the developing world.

In High-Income Countries, the Benefits of the Vaccine Outweigh its Costs

Rapid uptake of Hib conjugate vaccines has profoundly changed public health in the developed world. When the second-generation conjugate Hib vaccines were brought to market, the incidence of Hib disease plummeted faster than is typically seen when a new vaccine is introduced. By 2002, fewer than 100 cases of Hib disease were reported in the United States. This represents a greater than 99-percent reduction in disease burden. As far back as 1992, reduction of Hib-related morbidity and mortality was estimated to save the United States $500 million per year. The savings today are likely to be substantially greater, owing to the rise in health care costs and the sharp reduction in long-term care costs for disabled individuals.

As disease rates fell and the benefits of preventing cognitive and neurological sequelae grew, it became clear that the costs of Hib immunization were greatly outweighed by the vac-
cine’s health and economic benefits. Similar impact has been noted in other Western countries with high rates of Hib vaccination, such as Canada, the United Kingdom, Ireland, Austria, Spain, Switzerland, France, Germany, Finland, Netherlands, Scandinavia, Israel, and Iceland. Only three years after Iceland initiated its Hib vaccination program in 1989, no further cases of Hib disease were documented in that country. Hib disease, for all practical purposes, had been eradicated.

In the Developing World, Cost Is a Barrier to Adoption
Impact to date in the developing world has been much more modest—not because the vaccine does not work, but because few nations believe they can afford it. According to estimates based on several studies, Hib immunization efforts in poor nations have reduced the incidence of early childhood meningitis by only 6 to 8 percent. Inaction has carried a high price. In these countries, Hib disease kills an estimated 600,000 infants every year.

The problem is the vaccine’s cost. Its price—$2 per dose—plus the need to administer multiple injections on a set schedule make Hib conjugate vaccine too expensive for many poor countries to adopt. This is why, despite its exceptional effectiveness, four out of five countries tracked by the World Health Organization have not added Hib vaccine to their routine immunization programs.

A Comprehensive Vaccination Campaign Could Potentially Eradicate Hib Worldwide
Worldwide eradication of Hib might be possible if effective vaccination programs were established throughout the world. The biology of Hib makes it an apt target for eradication. Humans are the only host for Hib, so widespread use of the conjugate vaccine has the potential to end Hib disease across the globe. Adults do not need to receive repeat doses of Hib vaccine, as is typical of other protein vaccines, because their immune systems are stimulated on an ongoing basis by benign cross-reactive organisms. Thus, adults maintain protective levels of Hib antibodies throughout life. H. influenzae type b has not only shown no propensity to mutate into a vaccine-resistant form; it is highly unlikely to elicit resistance because the vaccine targets the polysaccharide that makes it pathogenic. Thus, eradication of this deadly and disabling disease is technically possible.

The principal obstacle is the vaccine’s cost and cumbersome administration schedule. In the United States, administration of Hib vaccine costs public payers an average of $5.23 and private health plans $18.65. A more efficient vaccine delivery schedule using smaller quantities of vaccine could make a difference for developing countries, but adoption would still be hindered by unreliable distribution, supply maintenance, and the complexities of administering multiple doses of vaccine.

Vaccine research continues in the hopes that production techniques will evolve in ways that maintain the extraordinary clinical value of the Hib vaccine while further reducing its costs. For example, instead of purifying Hib capsular polysaccharide from Hib bacteria, a biosynthetic version may be possible. This could enable production of anti-Hib conjugate vaccines on an industrial scale. A synthetic conjugate vaccine has already been found to be as safe and immunogenic as currently licensed Hib conjugate vaccines. Further research may reduce its cost.

Conjugate technology has enabled production of vaccines that have activity to other capsulated bacteria as well, including pneumococci, meningococci, group B streptococci, Salmonella typhi, and E. coli. In time, it may be possible to control or perhaps even eradicate
these pathogens as well. At this point in time, a host of candidate conjugate vaccines are being explored or are under development.66

**A Technology “Home Run”**

The CDC designated “vaccines universally recommended for children” as one of the United States’ ten great public health achievements of the 20th century.67 Hib is one of the leading agents on the CDC’s list.68 In a subsequent issue of the Morbidity and Mortality Weekly Report (MMWR Weekly) devoted to childhood immunization, the CDC concluded that, “In less than a decade, the use of the Hib conjugate vaccines nearly eliminated Hib invasive disease among [U.S.] children.”67

**The Best of the Best**

NICHD considers development of the Hib vaccine one of its greatest contributions to public health. The case of Hib conjugate vaccine development exemplifies the value of partnerships between public research agencies (the intramural and extramural research programs of the NIH’s NICHD and NIAID), public health (the CDC, which conducted important epidemiological and efficacy studies), the FDA (which reviewed and approved the marketing of both the first- and second-generation vaccines), and private industry (which provided the technical sophistication to develop additional protein conjugates, the resources to test them, and the production and marketing capacity to sell Hib conjugate vaccines throughout the United States, other high-income countries, and, perhaps in time, the developing world). Since Hib vaccine was brought to market, it has saved the lives of thousands of American children; sharply reduced the incidence of catastrophic Hib disease; and, by doing so, virtually eliminated the leading cause of acquired mental disability in the United States. This has spared countless families the heartache and costs of raising children with severe physical and cognitive disabilities.

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The Technology

Implantable cardioverter-defibrillators (ICDs) are designed to sense a life-threatening cardiac (heart) arrhythmia, such as ventricular tachycardia or ventricular fibrillation, and automatically provide a jolt of direct current (DC) electricity to covert the heart rhythm back to a normal heartbeat (normal sinus rhythm). In contrast to external defibrillators, such as the devices used in coronary care units, emergency departments, and the back of an ambulance, the components of an ICD are miniaturized so that they can be implanted inside a patient’s body.

The ICD is comprised of a pulse generator and one or more leads. The defibrillator lead is introduced transvenously and implanted inside the right ventricle of the heart. The lead has one or two coils at its tip and is able to deliver a series of high-energy shocks (5 to 30 Joules each) to the interior of the heart without damaging the heart muscle; an ICD’s leads also contain bipolar electrodes, which are used for ventricular pacing and sensing. Variations of the ICD include dual-chamber (atrial and ventricular) and biventricular (right and left ventricular) devices, which consist of additional leads to sense and pace the heart’s right atrium and left ventricle, respectively. The lead or leads are connected to a pulse generator, which is typically implanted in a pocket under the skin in the upper chest below the collarbone but outside the rib cage (see Figure 5.1).

A typical pulse-generator is approximately 5x5 cm—or about half the size of a smartphone—and consists of a battery, capacitors, and ports for the leads. Physicians can program the device to monitor abnormal heart rhythms using different thresholds and to deliver therapy, including antitachycardia pacing, to stop a dangerous tachycardia or deliver counter-shock therapy to terminate a potentially lethal cardiac arrhythmia. Current ICD models have the capacity to store electrograms, useful in determining whether patients received appropriate therapy (i.e., the defibrillator appropriately identified the abnormal heart rhythm as dangerous and delivered the correct treatment). The generator also collects and reports information on battery voltage, half-life, and lead impedance. Dual-chamber devices can detect atrial arrhythmias and pace the atrium, while biventricular devices synchronize pacing of the left and right ventricles (the two main pumping chambers of the heart) to improve cardiac output in patients with congestive heart failure and to overcome certain cardiac conduction delays—specifically, a form that impairs the ability of the left and right ventricles to work together. Typically, the battery of an ICD lasts four to nine years, at which point it must be replaced. The procedure is
ICDs were developed for the secondary prevention of sudden cardiac death (SCD), a condition caused by two particularly lethal types of cardiac arrhythmias—sustained ventricular tachycardia and ventricular fibrillation. Both cause sudden loss of consciousness and, if untreated, the latter almost invariably results in death within a few minutes. Most people who sustain an out-of-hospital cardiac arrest do not survive. In the United States, SCD is the leading cause of deaths due to heart disease, accounting for approximately 350,000 deaths annually.

Approximately 80 percent of people who suffer SCD have coronary heart disease. Men account for the majority of SCD cases (75%). Most are adults between the ages of 45–75 years. Major risk factors for SCD include left ventricular heart failure (systolic function ≤30–35%), hypertrophic or dilated cardiomyopathy, valvular heat disease, certain congenital heart anomalies, and primary electrophysiologic abnormalities.

ICDs have been shown to be effective in preventing SCD in persons with prior SCD who are found to have a nonreversible, continued risk for recurrent SCD. This is known as secondary prevention. ICDs have also been studied and found to be effective for the primary prevention of SCD, yet this group has generated much scientific and political debate (Box 5.1). Although a growing body of evidence supports the use of ICD therapy in selected patients with decreased left ventricular systolic function who have no history of SCD, it is not clear that all members of this much larger group will benefit, or that many would select treatment if they fully understood its potential benefits and risks.
Box 5.1
Indications for ICD Therapy in the Prevention of SCD

Secondary Prevention: Patients in this group have survived a prior cardiac arrest or sustained ventricular tachycardia. Additionally, patients with unexplained syncope thought to be due to ventricular arrhythmias are considered eligible for secondary prevention of SCD with an ICD.

Primary Prevention: Patients in this group have no history of SCD or sustained ventricular tachycardia but have a cardiac condition that places them at risk for SCD. By far, the largest group of patients who qualify for ICD therapy for primary prevention are patients with congestive heart failure. However, patients with congenital anomalies, other types of structural heart disease, and conduction defects may also qualify.

Development

The first DC defibrillator was developed in 1962 by Dr. Bernard Lown, a renowned physician-scientist who went on to become an equally accomplished humanitarian and social activist. Years after his groundbreaking work with defibrillators and anti-arrhythmics, Dr. Lown co-founded (along with Dr. Yevgeny Chazov of the former Soviet Union) International Physicians for the Prevention of Nuclear War. For their work, Drs. Lown and Chazov received the Nobel Peace Prize in 1985.

Initially, all defibrillators delivered DC countershocks through external paddles that were applied to the patient’s chest. Although their use was initially restricted to physicians, the treatment was so time-urgent that training programs were established to teach coronary care nurses and prehospital emergency medical services personnel (paramedics) to recognize a dangerous cardiac arrhythmia and attempt defibrillation or DC cardioversion.

In the mid-1980s, advances in microcomputers enabled manufacturers to produce automated external defibrillators (AEDs) that can accurately diagnose a dangerous cardiac rhythm and advise relatively untrained personnel, such as basic emergency medical technicians, firefighters, police officers, and even lay rescuers to deliver external countershocks through large adhesive electrodes applied to the victim’s chest. Although AEDs are much simpler to use than manual defibrillators, they still require an individual to recognize that a cardiac emergency has occurred, apply the electrodes, activate the device, and follow the automated prompts. Precious time can be lost while these steps are being accomplished. If no device is available at the time SCD occurs, the best that a bystander can do is perform CPR while emergency medical services rush to the scene. If the victim’s collapse is not observed, death almost always follows because treatment is started too late.

ICDs were conceptualized as a way to overcome these logistical shortcomings. Dr. Michel Mirowski, a Polish-born cardiologist who fled his country during World War II, conceived the idea for an implantable defibrillator in 1967, after a close friend and mentor died from recurrent bouts of ventricular tachycardia. Dr. Mirowski spent the next decade testing implanted defibrillator devices in dogs, with variable degrees of success. The first internal defibrillator was surgically implanted in 1980 at the Johns Hopkins Medical Center by Dr. Levi Watkins and Vivien Thomas, pioneering African American medical researchers. Thomas had previously worked as the lab assistant to Dr. Alfred Blalock, the surgeon who had designed the first proce-
Early Adoption

Within cardiology circles, the clinical trials that generated supporting evidence for use of ICDs are as well-known as the device's founders. (As is true of many drug trials, they are best known by the study's acronym.) Collectively, these studies define, for physicians and third-party payers alike, which patients are most likely to benefit from ICD therapy. Diffusion of ICD therapy for prevention of sudden cardiac death (SCD) can be benchmarked to the date on which each trial was published. Because ICDs were originally envisioned for secondary prevention of SCD, the data supporting this use case are reviewed first, followed by evidence for the far more expansive use of ICDs as a strategy for primary prevention of SCD.

Secondary Prevention of Sudden Cardiac Death

It has long been known that survivors of SCD due to ventricular fibrillation and patients who survive one or more bouts of sustained ventricular tachycardia are at very high risk for recurrent SCD. Two-year mortality rates vary from 20 percent to 45 percent, depending on the cohort. A series of secondary prevention trials conducted in the late 1980s to 1990s demonstrated improved survival among patients randomized to ICD therapy, though only one study had sufficient power to reach statistical significance. The three studies are Antiarrhythmics Versus Implantable Defibrillators (AVID),5 the Cardiac Arrest Study Hamberg (CASH),6 and the Canadian Implantable Defibrillator Study (CIDS) trials.7

AVID (1997)

In this study, supported by the National Institutes of Health’s (NIH’s) National Heart, Lung and Blood Institute (NHLBI), patients with a history of sudden cardiac death or ventricular tachycardia requiring cardioversion were randomized to treatment with an ICD or a class III antiarrhythmic drug, primarily amiodarone. Patients enrolled with a history of ventricular tachycardia also had to have an ejection fraction of less than 40 percent and to be symptomatic with heart failure. The trial was terminated early when a significant survival benefit was observed among the 507 patients randomized to the ICD arm as compared with 508 patients in the medication arm. The survival benefit persisted each year for three years: Relative risk reductions with ICD therapy compared with medication therapy were 39 percent, 29 percent, and 31 percent, p<0.02, respectively.

CASH (2000)

In this industry-sponsored trial, patients resuscitated from documented sustained ventricular arrhythmias (n=288) were eligible for inclusion and were randomized to ICD therapy or one of three antiarrhythmic medications (propafenone, amiodarone, or metoprolol). The primary
endpoint was all-cause mortality. Enrollment in the propafenone arm was terminated early after an interim analysis revealed a 61-percent higher mortality as compared with patients in the ICD arm. The other arms were followed for a mean of two years. There was a non-significant, 23-percent relative reduction in mortality in the ICD arm as compared with the combined amiodarone and metoprolol arms. However, the study was underpowered to find a significant effect if one existed.

**CIDS (2000)**

In this study, supported by a combination of government and industry funding, 659 patients resuscitated from one or more prior events of ventricular fibrillation, ventricular tachycardia, or unmonitored syncope with evidence of spontaneous (>10 seconds) or readily inducible ventricular tachycardia were randomized to therapy with an ICD or amiodarone. The primary outcome was all-cause mortality. Similar to findings in the CASH study, there was a non-significant, 20-percent relative risk reduction in mortality at five years among patients in the ICD arm as compared with the amiodarone arm. There was also a nonsignificant, 33-percent reduction in arrhythmic deaths.

A subsequent meta-analysis using data from these three trials was performed by Connolly et al. (2000). It revealed a cumulative 28-percent reduction (hazard ratio [HR] = 0.72; 95% confidence interval [CI] = 0.60–0.87, p = 0.0006) in the risk of all-cause mortality, almost entirely driven by a 50-percent decrease in the risk of arrhythmic death (HR = 0.50, 95% CI = 0.37–0.67, p<0.0001). Patients with a reduced systolic function, defined as an ejection fraction of less than or equal to 35 percent, benefited more than patients with preserved systolic function. The results of this meta-analysis and the three trials that informed it provide the empirical basis for the American Heart Association’s current guidelines for the secondary prevention of SCD (Box 5.2).

**Box 5.2**

**Class I Recommendations for ICD Therapy as Secondary Prevention in Patients with Heart Failure**

- ICD therapy is indicated in patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia after evaluation to define the cause of the event and to exclude any completely reversible causes (Level of Evidence: A).
- ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable (Level of Evidence: B).
- ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or ventricular fibrillation induced at electrophysiological study (Level of Evidence: B).

Primary Prevention of SCD

Because the pool of survivors of SCD and sustained ventricular tachycardia is relatively small, researchers examined whether ICDs might benefit patients at risk for this condition prior to the first such event. Since then, a series of trials have been conducted that demonstrate effectiveness in an expanding group of adults, all of whom have congestive heart failure and left ventricular systolic dysfunction.

In the late 1990s, two trials investigated the efficacy of ICD therapy in patients with underlying ischemic heart disease, the Multicenter Automatic Defibrillator Implantation Trial (MADIT)\(^9\) and the Multicenter Unsustained Tachycardia Trial (MUSTT).\(^{10}\)

**MADIT (New England Journal of Medicine, 1996)**

This industry-sponsored (CPI/Guidant) randomized controlled trial enrolled 196 patients with prior myocardial infarction (MI) (75 percent of whom had an MI less than six months prior to enrollment) who were deemed to be at high risk for ventricular tachycardia. Eligible patients had systolic heart failure with an ejection fraction less than or equal to 35 percent; nonsustained ventricular tachycardia; and inducible, nonsuppressible ventricular tachycardia on an electrophysiological (EP) study. Patients were randomized to ICD versus standard medical care (i.e., anti-arrhythmic medication), and average follow-up was 27 months. The primary endpoint was all-cause mortality. The mean age of patients was 63 years. The study detected a clinically and statistically significant decrease in mortality among patients randomized to ICD therapy (HR = 0.46, 95% CI = 0.26–0.82, p = 0.009).

**MUSTT (New England Journal of Medicine, 1999)**

This randomized controlled trial, supported by NHLBI and industry, studied a similar patient population as those included in MADIT, testing whether the strategy of performing an EP study to stratify patients at high risk of SCD was effective. The primary endpoint was cardiac arrest or death from a cardiac arrhythmia. Patients with prior MI; ejection fraction less than 40 percent; and spontaneous, nonsustained ventricular tachycardia were randomized to one of two arms: therapy guided by an EP study or no antiarrhythmic therapy. Patients in the first arm, who had inducible ventricular tachycardia on an EP study, received a staged protocol of anti-arrhythmic drugs, followed by ICD implantation if the medication failed.

At five years, patients with EP-guided antiarrhythmic therapy had a lower mortality than patients randomized to no antiarrhythmic therapy (relative risk [RR] = 0.73, 95% CI = 0.53–0.99); however, this difference was entirely driven by the subgroup of patients who received ICD therapy. Patients who received an ICD had a lower mortality than patients randomized to no anti-arrhythmic therapy and those who had an EP study that resulted in anti-arrhythmic medication but no ICD (RR = 0.24, 95% CI = 0.13–0.45).

**MADIT II (New England Journal of Medicine, 2002)**

In 2002, the findings of MADIT II were released.\(^{11}\) This trial extended evidence of the ICD’s effectiveness to patients with coronary artery disease and an ejection fraction less than or equal to 30 percent without requiring clinicians to demonstrate inducible ventricular tachycardia through an EP study. A total of 1,232 patients with a prior myocardial infarction and ejection fraction less than or equal to 30 percent were enrolled and randomized to receive a single-lead ICD versus conventional therapy. The primary endpoint was death from any cause. The mean age of patients was 64 years; nearly 90 percent had an interval of less than six months from their qualifying myocardial infarction. Over a mean follow-up period of 20 months, patients
enrolled in the ICD group had improved survival as compared with patients in the non-ICD, conventional therapy arm (HR = 0.69, 95% CI = 0.51–0.93, p = 0.016). As compared with MADIT, in which the mortality benefit for ICD therapy over conventional therapy was apparent immediately, the mortality curves for the two arms in MADIT II diverged only after one year.

**SCD-HeFT (New England Journal of Medicine, 2005)**
The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) further extended evidence of the value of ICD therapy to patients with and without ischemic heart disease as the underlying cause of systolic heart failure. It serves as the basis for current guidelines and payment coverage in this population. This randomized trial, which was sponsored by the NHLBI and industry, is notable in that it examined patients with and without coronary artery disease who had systolic heart failure with an ejection fraction less than or equal to 35 percent. It randomized 2,521 patients to standard heart failure therapy, plus either placebo, shock only/single-lead ICD, or amiodarone. The primary endpoint was death from any cause, and the mean follow-up period was 45.5 months. The mean age of patients was 60 years, and nearly half of the patients enrolled had no history of coronary artery disease. As compared with placebo, amiodarone was associated with a similar risk of death (HR = 1.07, 95% CI = 0.86–1.83, p = 0.53); ICD therapy was associated with a lower risk of death (HR = 0.77, 0.62–0.96, 0.07). Of note, the mortality curves for the three arms did not diverge until approximately 20 months.

**DEFINITE (New England Journal of Medicine, 2004)**
One year later, the less definitive Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was released. Patients with nonischemic cardiomyopathy and an ejection fraction less than or equal to 35 percent (n = 458) were randomized to standard care versus standard care plus ICD implantation. The primary endpoint was all-cause mortality. At two years, the ICD group had a nonsignificant reduction in mortality compared with the medical therapy arm (8.1 percent versus 14.1 percent, p = 0.06). The authors speculated that the unexpected high rates of nonarrhythmic death in both groups contributed to the study being underpowered to find a difference in arrhythmic deaths. Interestingly, the sponsor of the study is not mentioned in the article or accompanying disclosures. Although the study was published in a respected, peer-reviewed journal, it is not listed like the others on clinicaltrials.gov.

While the primary endpoint in most of the clinical trials evaluating ICD therapy was all-cause mortality, the prevention of arrhythmic deaths drives the effect. In the DEFINITE trial, the authors argued as much when they noted that the nonsignificant association of ICD therapy with all-cause mortality was due to an unexpectedly low occurrence of arrhythmic deaths in both treatment and control groups.

The counterargument is that clinical trials are supposed to determine effectiveness. From the patient’s point of view, death is death, regardless of the cause. This is particularly germane when an ICD is implanted in a patient with severe disease, such as nonischemic cardiomyopathy and low ejection fraction. Although it is accepted practice to implant ICDs, a close look at the evidence reveals discordant findings.

**Not All Groups Benefit from Receiving ICDs**
There are subgroups for whom ICD therapy provides little or no benefit. Based on these trials, ICDs should not be implanted in the immediate 40 days following acute myocardial infarction.
or in the three-month period following coronary artery bypass surgery or percutaneous transcatheter coronary angioplasty. These studies include the Coronary Artery Bypass Graft Patch Trial (CABG-Patch), the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), and the Immediate Risk-Stratification Improves Survival (IRIS) trials.

**CABG-Patch (New England Journal of Medicine, 1997)**
In this study, supported by NHLBI and Guidant/CPI, patients undergoing coronary artery bypass surgery who had an ejection fraction less than or equal to 35 percent and an abnormal signal-average electrocardiogram were randomized to receive an ICD during surgery versus no ICD. The primary endpoint was all-cause mortality. Among 1,055 patients, there was no evidence of improved survival among patients receiving ICD therapy (HR = 1.07, 95% CI = 0.81–1.42, p = 0.64).

**DINAMIT (2004)**
224 patients with recent MI (6 to 40 days post-MI), ejection fraction less than or equal to 30 percent, and reduced heart rate variability by Holter monitor were randomized to ICD versus no ICD. The primary endpoint was death from any cause. Mean follow-up was 30 months. While there were fewer deaths due to arrhythmias in the ICD group, all-cause mortality did not differ (HR = 1.08, 95% CI = 0.76–1.55).

**IRIS (2009)**
This trial enrolled a similar population of patients as the DINAMIT trial, with nearly identical results. Specifically, 898 patients early post-MI, with ejection fraction less than 40 percent and either HR >90 or nonsustained ventricular tachycardia, were randomized to ICD versus no ICD. Similar to the results of DINAMIT, there was a decreased risk of death due to arrhythmia in the ICD group, but no overall survival benefit for patients with ICD (HR = 1.04, 95% CI = 0.81–1.35).

Collectively, these trials form the basis for current AHA guidelines for primary prevention of SCD (Box 5.3).

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**Box 5.3**

**Class I Recommendations for ICD Therapy as Primary Prevention in Patients with Heart Failure**

- ICD therapy is indicated in patients with an LVEF ≤35% due to prior MI, who are at least 40 days post MI, and who have NYHA Class II or III (Level of Evidence: A)
- ICD therapy is indicated in patients with an LVEF ≤35% due to non-ischemic cardiomyopathy, and who have NYHA Class II or III (Level of Evidence: B).


NOTES: LVEF = left ventricular ejection fraction, MI = myocardial infarction, NYHA = New York Heart Association, VT = ventricular tachycardia.
Limitations of Clinical Trials

Although current guidelines for use of ICDs are based on clinical trial data, participants in clinical trials do not always resemble the community-based populations that subsequently receive treatment. Clinical trials enroll carefully selected study candidates and typically manage them under ideal conditions that are difficult to replicate in community settings. Certain patient subgroups (e.g., the elderly and patients with multiple comorbidities) are often underrepresented in clinical trials. For this reason, ICD therapy may not be appropriate for some patients who technically meet American Heart Association (AHA) guidelines.

Subsequent Use

Because ICDs are expensive (the typical price is about $20,000–$30,000), and their implantation is costly as well (typical procedure fees are about $35,000), diffusion has been largely driven by whether or not public and private payers will reimburse for the technology and its use. Without insurance coverage, few patients could afford an ICD. And because private insurance companies generally follow the lead of Medicare, the Centers for Medicare and Medicaid Services (CMS) has played a highly important role in enabling the diffusion of ICDs.

Once ICDs were shown to be beneficial in the relatively small number of individuals who survive a prior episode of SCD or protracted bouts of ventricular tachyarrhythmia, Medicare’s decision to cover their use in this patient population was relatively straightforward. This is why, only one year after the FDA approved the sale of ICDs, CMS issued its first Medicare National Coverage Determination (NCD) in 1986.

Because the benefits were less clear-cut and the financial consequences were much greater, the decision regarding whether or not to expand coverage of ICD therapy from secondary to primary prevention was much more controversial. Nevertheless, as more clinical trials were reported, CMS expanded its coverage policies in 1991, 1999, 2003, and 2004.

Medicare Expands Coverage to Include Primary Prevention

A pivotal moment occurred in 2003, when the Medicare Coverage Advisory Committee (MCAC) convened to discuss ICD therapy for primary prevention. At the time, the results of MADIT-II were available; however, the SCD-HeFT trial, which was testing ICD therapy in an expanded population, was still ongoing. MCAC recommended adopting the same inclusion and exclusion criteria as the MADIT-II trial, which included patients with ischemic heart disease and reduced systolic function (ejection fraction less than 30 percent).

Concerned by the cost implications of offering ICDs to such a large number of patients, CMS ultimately opted to cover ICDs to a subgroup of the MADIT-II population, which the analysis suggested would derive the most benefit. Many in the research and clinical communities objected to this decision, since subgroup analyses are prone to bias and random effects. Others questioned whether MADIT-II provided sufficient evidence to move forward with expansion of coverage. The remarks of Mark Hlatky, who presented to CMS, illustrate this perspective:

I think the big question is whether an EF below 30 percent in and of itself is sufficient to put in an ICD, and I would say that the question here is whether the evidence is adequate. I would say MADIT II is suggestive, it’s highly suggestive, but it doesn’t really prove the
case completely for this. The word that was used earlier by Dr. Moss and the representative of the company was a paradigm shift, a paradigm shift to say that we don’t need any additional markers of patients with low EF. And I question that because this is a single study; it’s very well done, but it’s only a single study. And I think we have 25 years of research that says that there are other markers that are important and for that reason I am concerned that an indication from Medicare that says that ejection fraction alone is necessary to put in an ICD is overly broad, and would expose many patients who would not benefit from this device to risks, to say nothing of the large costs to the program.21

Another public presenter, Dr. Joanne Lynn, had similar concerns:

In sum, I would recommend that the Medicare Coverage Advisory Committee do the following: First, advise CMS to issue a national coverage determination for ICDs only for the populations where evidence is strong that they actually gain desired outcomes, which may mean that only a very small part of the Medicare population should be covered now, and certainly does not now include elderly who have multiple comorbidities and competing causes of death. Second, we should call on CMS to insure that Medicare patients have a high standard of informed consent. We should recommend that CMS institute methods to monitor outcomes, that they require evidence about all of the outcomes, including quality of life. That they monitor changes in the performance over time, and call on various parties to take up discussion of the priorities and values that are at stake.

As CMS was considering this cautionary testimony, Medtronic Inc. released preliminary data from the SCD-HeFT trial, which included patients with ejection fractions less than or equal to 30 percent due either to nonischemic or ischemic heart disease. Based on these findings, the company pressed CMS to expand coverage to include a larger group of patients. In the course of considering Medtronic’s request, CMS met with the makers of the other ICDs, including Boston Scientific and Guidant, as well as the Heart Rhythm Society and the American College of Cardiology. Additionally, they solicited public comment on three separate occasions. Ultimately, CMS determined that ICDs were “reasonable and necessary” for primary prevention of SCD in patients with a reduced ejection fraction due either to ischemic or non-ischemic heart failure.22 This decision dramatically expanded the number of patients eligible for ICDs.

**Medicare Approves Further Expansion but Specifies “Coverage with Evidence Development”**

To ensure that its decision produced the benefits that manufacturers and experts promised, CMS added an important caveat to its decision: It would reimburse providers for ICD implantations, but only if patients who received an ICD for primary prevention of SCD were enrolled in an FDA-approved clinical trial, a clinical trial managed by CMS, or another organization’s approved treatment registry.23 The policy, known as “coverage with evidence development,” is similar to the FDA’s “accelerated approval” process (see the case study in this appendix on Avastin for metastatic breast cancer).

To help its members comply with CMS’s requirement, the American College of Cardiology established an ICD registry under the National Cardiovascular Data Registry (NCDR). This registry began collecting data in 2006. Hospitals are only required to submit data to NCDR on ICD implants involving Medicare beneficiaries. However, less than 75 percent of
participating hospitals report data on all of their ICD implantations, including those provided to privately insured patients.

As a result of progressively expanded coverage, implantations of ICDs grew by 20–30 percent annually between 1985, the year ICDs secured FDA approval, and the mid-2000s.24 A total of 415,780 ICDs were implanted in the 12-year interval between 1990–2002.25 In the four years between 2006–2010, over half a million ICD implants were registered in the National Cardiovascular Data Registry, which captures 90 percent of ICDs implanted in the United States. This prodigious growth was primarily driven by the expansion of coverage to primary prevention of SCD, which now accounts for four out of every five ICD implants.

Interestingly, despite Medicare’s decision to further expand the range of patients eligible for ICDs in 2005, sales of devices started to decline the following year. They have continued to fall through 2012, the most recent year for which data are available.26 The reasons for this trend are not entirely clear. There are plenty of eligible patients; Hernandez et al. noted in 2007 that only 35 percent of hospitalized patients with a class I indication for ICD therapy have received an ICD or had a plan for future implantation.27 Women and African American patients with class I indications were less likely to receive ICD therapy than white men, even after controlling for age, insurance status, and comorbidities.

The decline in enthusiasm for ICD therapy may, in part, reflect (1) growing recognition that the types of patients who are being treated today with ICD therapy are quite different than the patients who participated in the original clinical trials, so the effectiveness of ICD treatment in these populations may be less; (2) growing recognition that the devices can inappropriately deliver one or more shocks without warning (i.e., the device falsely senses an arrhythmia and tries to treat it; ICD shocks, particularly false ones, are painful, costly, and substantially degrade a patient’s quality of life); and (3) growing fears of legal liability from complications of treatment (such as infection) and device malfunctions due to lead failures.28

ICDs Are Sometimes Implanted in Patients Who Are Unlikely to Benefit
Today, more than 40 percent of ICDs are implanted in patients over 70 years of age. Approximately 10 percent are implanted in patients 80 years of age or older.29 This age distribution is older than that of the early clinical trials establishing the efficacy of ICDs for prevention of SCD. In the SCD-HeFT trial, which is the basis for current treatment guidelines and CMS payment policy, approximately a third of subjects were 65 years of age or older, and 9 percent were over 75 years of age.

ICD implantation is less beneficial in older patients than younger ones. In the MADIT-II trial, patients over 65 had less risk reduction, and in the SCD-HeFT trial, the older age group had no survival benefit from ICD implantation. Even when data were pooled in a meta-analysis combining data from MUSST, MADIT-II, DEFINITE, and SCD-HeFT, ICDs were associated with a nonsignificant trend of lower all-cause mortality in the age 65 and older group (n = 3,562, HR = 0.66, 95% CI: 0.5–0.87, p = 0.15) that became statistically significant in the over age 75 group (n = 579; HR = 0.73, 95% CI 0.51–0.97, p =–0.03). However, this study found no evidence that ICDs improved rates of survival in older patients from SCD, the condition the devices are intended to treat.

Based on the findings of clinical trials, AHA guidelines recommended against implanting ICDs in certain clinical contexts. Unfortunately, clinicians often disregard this guidance. For example, the AHA’s guidelines recommend against ICD therapy in patients who are undergoing bypass surgery or in the early period after a myocardial infarction (because there is no
clinical benefit). The guidelines also advise against ICD use in the first three months following coronary revascularization and in patients with New York Heart Association (NYHA) class IV symptoms or newly diagnosed heart failure (populations that were excluded from the above clinical trials). Despite the clarity of this guidance, a recently published study showed that among 25,000 patients who received an ICD and were enrolled in the National Cardiovascular Data Registry-ICD Registry, nearly one in four—22.5 percent—received an ICD for a non—evidence-based indication.19

In Canada, ICD implants are more restricted than in the United States because of their high cost. As a result, only about a fifth as many eligible patients receive ICD therapy in Canada as in the United States.30 The impact of these differences on outcomes has not been examined.

There is emerging evidence that high-risk, “real-world” patients treated in community settings derive similar benefits to those documented among participants in clinical trials. For example, Chan et al. analyzed a prospective cohort of 965 “real-world” patients with ischemic and nonischemic heart failure enrolled in a multisite registry.31 They found that ICDs were effective in reducing mortality and that the magnitude of risk reduction was similar to that observed in clinical trials (HR = 0.69, 95% CI = 0.05–0.96, p = 0.03). Furthermore, they found that the survival benefit persisted in patients of all age groups, including those over age 75, as well as in patients with multiple comorbidities.32 An analysis of Medicare beneficiaries hospitalized for heart failure during 2003–2005 compared patients with heart failure and an ICD with a propensity score—matched group of patients hospitalized for heart failure but with no ICD.19 The mean age was 76 years in the ICD group and 77 years in the non-ICD group. Similarly, the authors found a significant survival benefit among patients with an ICD (HR = 0.62, 95% CI = 0.58–0.67). The authors concluded that ICD therapy provides substantial health benefits to Medicare beneficiaries.

Interestingly, both of these studies conclude that although patients of older age and greater comorbidity burden are at a higher risk for all-cause mortality, this does not preclude them from deriving benefit from ICD therapy. In fact, the absolute risk reduction in these high-risk populations may be greater. The authors acknowledge, however, that the cost-effectiveness of ICDs in these high-risk patients is less, due to the substantially higher rate of all-cause mortality.

Despite evidence that ICDs can benefit appropriately selected elderly patients, there is little enthusiasm for the technology in this age group.33, 34 One reason is the concept of “competing mortality”—the realization that as patients grow older, they may die from a cause unrelated to their ICD. Yung et al. evaluated rates of overall mortality in a prospective cohort of adults who received ICDs in Ontario, Canada.35 They found increasing risk of mortality in each respective age group, although the rates of appropriate shocks were similar in each cohort. A recent analysis determined that a third of Medicare recipients who received an ICD for primary prevention died within three years of implantation. In this study, the number of hospitalizations for heart failure was highly predictive of prognosis. Among patients with no prior hospitalizations, the three-year mortality rate was 27 percent. It was 63 percent in patients with 3 or more prior hospitalizations.36
Health and Cost Impact

ICDs are intended to recognize and automatically treat life-threatening arrhythmias, namely ventricular tachycardia or fibrillation. As noted in earlier sections, they have been shown to significantly reduce rates of death from SCD when implanted in properly selected patients.\(^{12,37}\) Although one might expect, given the large number of devices implanted over the last 20 years, that ICDs have had a favorable impact on population rates of SCD, there are no published studies that quantify the contribution of this technology to an overall change in the incidence of this condition.

Inappropriate Shocks

Although the literature indicates that ICDs have benefited many patients who had them implanted, they are not risk-free. Sometimes, the decision to implant an ICD leads to serious complications or side effects. For example, an ICD may falsely identify other, nonfatal arrhythmias (e.g., atrial flutter or sinus tachycardia) as ventricular arrhythmias and inappropriately deliver painful shocks. Both appropriate and inappropriate shocks are common, though their frequency varies depending on the patient’s baseline risk for ventricular arrhythmias. Newer ICD programming has improved rhythm detection, but it has not entirely eliminated this problem. In the AVID trial for secondary prevention, rates of ventricular arrhythmias and subsequent shock therapy were 35 percent at three months, 53 percent at one year, and 68 percent at two years. Among 194,100 patients who received an ICD for either primary or secondary prevention and were enrolled in a telemonitoring system by Boston Scientific, 23 percent received one or more inappropriate shocks, and 17 percent experienced one or more inappropriate shocks within five years of implantation.\(^{38}\) The declining rate of delivered shocks reported in recent studies probably reflects the greater proportion of implantations for primary prevention of SCD (currently, about 80 percent).\(^{1}\) Heart failure patients have a higher risk of cardiac arrhythmias than age-matched normal patients, but it is much lower than the risk among patients who have had a prior SCD or bout of ventricular tachycardia.

Irrespective of whether a shock is appropriately delivered or not, it is painful and, for some, terrifying. Patients frequently liken the sensation to “being kicked by a mule” or “an earthquake.” Often, the recipient’s quality of life and health are negatively impacted.\(^{39}\) Compared with ICD patients who have never been shocked, those who experience one or more ICD shocks have higher rates of anxiety and depression. Receiving ICD shocks is also associated with an increased risk of hospitalizations and subsequent mortality, most likely because delivery of a shock is an indicator of more advanced disease. Speculation that shocks produce myocardial injury has not been borne out.\(^{38}\)

Surgical Complications

ICD implantation is associated with both periprocedural and long-term adverse events. During hospitalization for ICD implantation, there is an approximate 3-percent risk of having a complication, the most common being lead dislodgement (1%), hematoma (0.9%), pneumothorax (0.4%), and cardiac arrest (0.3%). The risk of these events is higher if a dual chamber or a biventricular device is placed because these are more complicated procedures.\(^{40,41}\) ICDs implanted by non–electrophysiology-trained cardiologists and by thoracic surgeons are associated with higher complication rates than those implanted by electrophysiology specialists.\(^{1}\) Additionally, cases in which an ICD is placed for a non–evidence-based indication are also
associated with higher complication rates. It is possible that these trends are collinear, but this has not been proven.

Infection
Infection of the subcutaneous pocket that holds the ICD or the device’s intracardiac leads (resulting in endocarditis) occurs in approximately 1–3 percent of implantations. Studies indicate that the rates of infection are rising. In 2008, the rate of infection was 2.8 percent, as compared with 1.5 percent in 2003. The increase in infections is attributed to the expanded use of ICDs in patients with multiple comorbidities because sicker patients are more prone to infections. An infection of an ICD is costly, both to the patient and to the health care system. Frequently, treatment requires protracted administration of powerful intravenous antibiotics and perhaps surgery to replace and or remove infected leads and/or the pulse generator. The societal costs of an iatrogenic infection are approximately $146,000 per case.

Lead Failures
Fractures in an ICD lead, problems with lead insulation, and other device malfunctions can result in undersensing of ventricular arrhythmias or detection of false signals, which trigger inappropriate shocks. The true rate of lead failure is unknown, though it has been estimated to occur at a rate of 0.5 percent per year. The Guidant Endotak DSP (model 0125) and the Medtronic Transvene (model 6936) were found to have high lead failure rates. Two recent recalls of the Medtronic Fidelis Lead (2007) and the St. Jude Riata lead (2011) have raised awareness among both patients and clinicians of the problem of lead failures. In the case of the Medtronic lead, there were two fracture sites along the conductor that were responsible for high rates of inappropriate shocks and preventable death. The Fidelis lead was implanted in 205,600 patients in the United States, less than a quarter of whom had the lead extracted. This leaves approximately 150,000 Fidelis leads in active use. While these widely publicized recalls have been implicated as a reason for the decline in ICD implants, research shows that the trends were already occurring and that lead recall did not significantly impact utilization.

Are ICDs Cost-Effective?
If, as is widely assumed, ICDs implanted for primary prevention produce the same survival benefits observed in the published clinical trials, the estimated cost of implanting an ICD for primary prevention of SCD is between $34,000 and $72,000 per quality-adjusted life year (QALY) gained. While this cost is high, it is in the general ballpark with the cost of treating end-stage renal disease, which Medicare has used as a reference point for comparisons of cost-effectiveness. Using mortality results from the SCD-HeFT trial as a reference, another analysis estimated the cost of an ICD to be $38,389 per life-year saved. An analysis among Medicare beneficiaries found that treatment of ICD recipients cost $41,542 more in the first 30 days following implantation than propensity-matched heart failure patients who were hospitalized but did not receive an ICD. This cost difference persisted for up to a year, with relatively little incremental costs after the initial hospitalization and the immediate 30-day follow-up period.

There are, however, limitations to the cost-effectiveness studies conducted to date. None of these analyses has factored in the cost of potential complications or the impact of complications, such as infection or inappropriate shocks, on quality of life. One can easily imagine that the cost of caring for a patient with multiple inappropriate shocks, especially if that person...
was nearing the end of life, would be much greater than that reflected in a simple cost-benefit analysis.

A second concern is that the cost-effectiveness analyses produced to date were based on the assumption that a single-chamber ICD device was used. However, in the United States today, more than two-thirds of patients receive a far more expensive dual-chamber device, which involves the placement of an extra atrial lead. Although the placement of an atrial lead is useful in the relatively few patients who require atrial pacing, six out of ten patients who receive a dual-chamber device do not need the extra lead or the device’s added complexity. Advocates of dual-chambered devices say that they implant them based on theoretical benefits of improved rhythm interpretation, perhaps resulting in fewer inappropriate shocks and enhanced efficiency, should there ever be a future need for pacing.

However, contrary to these beliefs, dual-chamber devices have not been shown to improve outcomes. They are also associated with more complications than less expensive single-chamber devices.40

“Treatment Creep”

ICDs represent the technical prowess of American biomedical engineering. They have benefited thousands of Americans, many of whom might not be alive today without them. Rigorous, prospective randomized trials involving carefully selected groups of patients have consistently demonstrated a 30–40-percent relative risk reduction in mortality at a cost per QALY comparable to that of renal dialysis. This progress has come at a cost: Annual expenditures for ICD therapy are estimated to be $4.6 billion per year, accounting for approximately 100,000 annual ICD implantations. It has been estimated that if all of the 500,000 people who meet current clinical guidelines for implantation of an ICD got one, annual expenditures would rise to $15 billion.23, 48, 49

Unlike many therapies that slowly penetrate the marketplace, ICDs quickly worked their way into clinical practice. The rapid diffusion of the technology was likely driven in part by a series of positive clinical trials, in part by manufacturer encouragement, and, most importantly, by the willingness of CMS to progressively expand the population of patients who qualify for coverage.

Professional societies and groups like the AHA have attempted to place reasonable boundaries on the use of ICDs. For example, they endorse consideration of ICD therapy for primary prevention only when patients are receiving optimal medical therapy, have at least one year of life expectancy, and are in good functional health. However, defining the life expectancy of a patient with heart failure is notoriously difficult, particularly in older adults.

Unfortunately, these guidelines are often ignored. For example, experts recommend against ICD therapy in patients who are undergoing bypass surgery or in the early period after a myocardial infarction. They also advise against implanting ICDs in the first three months following coronary revascularization, in heart failure patients with severe (i.e., NYHA class IV) symptoms, and those with newly diagnosed heart failure. Nevertheless, a recently published study found that 22.5 percent of roughly 25,000 patients enrolled in the National Cardiovascular Data Registry-ICD Registry received an ICD for a non–evidence-based reason.50 Those who inappropriately received an ICD had a higher rate of in-hospital mortality and more periprocedural complications than patients who received guideline-concordant treatment.
Studies like this would not be possible without CMS’s “coverage with evidence development” policy that requires certain costly technologies, such as ICDs, to contribute data to registries to monitor utilization, track outcomes, and identify safety concerns (such as device malfunction). The policy should be used more often to monitor such costly technologies as orthopedic implants and proton beam therapy.

The finding that many ICDs are inappropriately implanted also argues for active involvement of patients in decisions about the pros and cons of implanting an ICD. Early on, patient information literature on the technology lacked balance. Cardiologists who only follow clinical guidelines, rather than considering patient preferences, could also push some patients to accept a treatment they later regret. This may explain why many heart failure patients feel inadequately informed about the prognosis of their disease and the ability of an ICD to extend their life.

With increasing data on the effectiveness of ICDs, cardiologists can provide more-individualized assessments of likely benefits and risks. Matlock et al. are developing and testing “decision aids” intended to help patients understand available data about benefits and trade-offs and weigh their own preferences about ICD implantation. Respecting a patient’s values and preferences regarding ICD implantation (and its subsequent deactivation) can improve outcomes and reduce unwanted costs.

More must be done to deter inappropriate implantations, as well as the inappropriate use of more costly dual-chambered devices that offer no added benefit to patients and may even increase the risk of harm. However, in carefully selected patients, implantation of an ICD saves lives at a price per QALY in line with other costly but widely accepted life-sustaining technologies, such as renal dialysis. The challenge with ICDs and other high-cost, high-technology devices like them is limiting their use to patients who are most likely to benefit.

References


Case Study 6

Prostate-Specific Antigen

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The Technology

Prostate-specific antigen (PSA) is a protein secreted by the prostate gland. Low levels of PSA are present in the serum of all men, but elevated serum PSA levels correlate with a higher likelihood of having prostate cancer.

Rationale

PSA was initially discovered in the course of forensic research on techniques to identify seminal fluid in cases of suspected rape. In the early 1980s, elevated serum levels of PSA were found to correlate with prostate cancer, and PSA began to be used as a biomarker of prostate cancer. In the late 1980s, the level of PSA was shown to be proportional to increasingly palpable prostate cancer on digital rectal examination. It was also shown to correlate with higher clinical stages of prostate cancer. In 1994, the U.S. Food and Drug Administration (FDA) approved PSA as a screening test for prostate cancer.

Although the PSA blood test is widely used today, it has drawbacks. PSA is sensitive (meaning that it is almost always abnormal in prostate cancer), but it has very low specificity (meaning that the test is often abnormal, even in men who do not have prostate cancer). Moreover, prostate cancer is ubiquitous, with a lifetime risk of 1 in 6. Cases of prostate cancer vary widely in terms of growth rate and aggressiveness. In some men, the disease is so indolent that it is incidentally identified after death from an unrelated cause.

Initially hailed as a highly useful cancer screening test, that value of PSA has recently been reassessed as the costs and consequences of needless biopsies and treatment are tallied. Nevertheless, 25 million PSA screening tests are ordered every year. Richard J. Albin, an early PSA investigator, recently remarked, “I never dreamed that my discovery four decades ago would lead to such a profit-driven public health disaster.”
Development

Development of the serum test for PSA can be traced to work conducted in the laboratory of Professor T. Ming Chu at Roswell Park Memorial Institute (now Roswell Park Cancer Institute) in the late 1970s. Financial support for this line of research was provided in part by the National Cancer Institute as part of the National Prostate Cancer Project. In 1979, investigators reported the discovery and purification of a protein isolated using rabbit-derived antiserum, terming the substance prostate-specific antigen. Subsequently, Papsidero and colleagues, from the same research group, described experiments identifying PSA in the serum of patients with metastatic prostate cancer. In 1981, the group followed with a report documenting the potential utility of using PSA to monitor treatment response in patients with prostate cancer. These investigations and others resulted in a patent issued to Roswell Park and the state of New York in 1984.

The technology was subsequently transferred to the biotechnology industry in order to develop a commercially available serum test. In 1986, Hybritech received FDA approval for the PSA Tandem-R assay for the monitoring of treatment and recurrence among patients already diagnosed with prostate cancer. FDA approval of the PSA test for the purpose of screening asymptomatic men for prostate cancer did not occur until 1994.

Early Adoption

PSA Testing First Used to Monitor Treatment

The first clinical application of the newly developed PSA test was for monitoring (not detection) of prostate cancer. The Roswell Park group contributed a number of studies that linked changes of PSA levels with disease stage, treatment response, disease recurrence, and progression. In a landmark study, Stamey and colleagues reported the results of a study testing 2,200 serum samples from 699 patients, among whom 378 carried a diagnosis of prostate cancer. They found that PSA levels were elevated in most men with previously undiagnosed prostate cancer. In addition, PSA level correlated with cancer stage. Moreover, it dropped to low or undetectable levels following surgical prostate removal. Finally, PSA was useful in detecting residual as well as recurrent prostate cancer in men undergoing treatment for the disease. Based on these studies, the PSA test was applied in clinical practice.

FDA Approval for Screening Use Followed

Soon after the test's adoption, other investigators focused on its potential use for detecting prostate cancer in asymptomatic men. One of the leading proponents of PSA screening for prostate cancer during this period was William J. Catalona. In a landmark 1991 paper partially funded by Hybritech, a division of Eli Lilly & Company, Catalona's group demonstrated that PSA combined with digital rectal examination was a superior method of detecting otherwise asymptomatic prostate cancer compared to examination alone.

On the basis of these findings and those of other investigators, in 1994 the FDA approved the PSA test for the purpose of screening asymptomatic men for prostate cancer. However, even in these early days, concern existed in the medical community about the ethics, benefits,
and potential harms of widespread PSA screening. This presaged the current debate about the utility of population-based screening.

Subsequent Use

Even before FDA approval of PSA as a screening test, its use skyrocketed among cancer-free men. Among men aged at least 65 years, PSA testing rose from less than 5 percent of white men in 1989 to approximately 40 percent in 1994; in black men the rate rose from a similar baseline to approximately 35 percent in 1994.

By the early 1990s, the rapid growth and widespread use of PSA testing produced a sharp spike in the prevalence of detected disease (Figure 6.1). This increase was not due to a rising incidence of prostate cancer; rather, it reflected a sharp increase in the detection of previously unknown and generally localized prostate cancers in otherwise asymptomatic men.

Professional Organizations Provide Strong Support

In the mid-1990s, momentum for the use of PSA as a prostate cancer screening test continued to build. This was due, in large part, to the efforts of the American Urological Association and the American Cancer Society, both of which recommended screening with PSA even before FDA approval, and such organizations as the National Comprehensive Cancer Network and National Cancer Institute, which recommended PSA screening after it was FDA-approved. Stimulated by this support, legislation at the state and federal level enshrined receipt of an annual PSA test as a legal right. For example, Section 4103 of the 1997 Balanced Budget Act mandated federal coverage for prostate cancer screening tests (e.g., the PSA test). The resulting

Figure 6.1
Prostate Cancer Incidence Trends (1975–2006)

*Rates are age adjusted to the 2000 US standard population

Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, 1973-2006, Division of Cancer Control and Population Science, National Cancer Institute, 2009. Data for whites and African Americans are from the SEER 9 registries and are adjusted for delayed reporting. Data for other race/ethnicities are from the SEER 13 registries and are not adjusted for delayed reporting, and thus data for the most recent years are likely to be underrepresented. For Hispanics, incidence data do not include cases from the Alaska Native Registry. Incidence data for American Indians/Alaska Natives are based on Contract Health Service Delivery Area (CHSDA) counties.

national coverage determination from the Centers for Medicare and Medicaid Services took effect on January 1, 2000.

Corporate and Nonprofit Lobbying Promotes Use
Industry involvement in promoting PSA testing drove uptake higher. Since 2000, the annual frequency of PSA screening has nearly doubled. In 1992, even before the FDA had approved PSA as a screening test, TAP Pharmaceuticals, which at the time was a manufacturer of a prostate cancer treatment, sponsored St. Louis Cardinals star Stan Musial, a three-time National League MVP and first-ballot Hall of Fame Inductee, to promote “Prostate Cancer Awareness Week.” TAP and other pharmaceutical companies also contributed to such patient advocacy groups as “Us Too,” which lobbied the National Cancer Institute to promote PSA testing. Other celebrity advocates of PSA screening included Harry Belafonte, Arnold Palmer, Joe Torre, and John Kerry. Gen. Colin Powell served as a spokesman for the Prostate Cancer Education Council, which sponsors Prostate Cancer Awareness Week. In 2009, Kimberly-Clark started the “Depend Campaign to End Prostate Cancer,” which featured endorsements from such athletes as Jim Kelly, Ozzie Smith, Mike Bossy, Rod Woodson, Len Dawson, and Ken Griffey, Sr. It also sponsored “Men's Health Month” to encourage prostate cancer screening. Depend, a product for adult incontinence, is one of the company's leading sellers.

Cost and Health Impact
Prostate cancer is common, but the course of the disease is extremely variable. The lifetime risk of developing prostate cancer is approximately 1 in 6; however, the lifetime risk of death from prostate cancer is only 1 in 30.25 The reason for prostate cancer’s relatively low mortality rate is that many cases involve low-level disease, or that the patient is so elderly at the time of diagnosis that he dies from an unrelated health problem, such as heart disease, before the cancer spreads. An incidental finding of prostate cancer is made in up to 45 percent of men undergoing surgical removal of the bladder and prostate for bladder cancer.26–30 Since the introduction of PSA screening in the late 1980s, prostate cancer has been diagnosed at progressively earlier stages and at less-advanced grades with increased frequency.31 Because low-risk prostate cancer often follows an indolent clinical trajectory,32 the overall survival benefit of curative management of prostate cancer as a whole is small and is limited to men with more-aggressive disease.33–35

Although Watchful Waiting Is an Acceptable Option, Few Men Choose It
Men diagnosed with prostate cancer are typically offered one of three options: radical prostatectomy (surgery), radiation therapy (either via external beam or radioactive inserts), or active surveillance (also called “watchful waiting”). Active surveillance entails periodic PSA testing, digital rectal examinations, and prostate needle biopsies at predetermined intervals, although the ideal interval is unknown.36–44 Despite the absence of demonstrated superiority of curative treatment over active surveillance among men with low-risk prostate cancer, population-based studies suggest that only one-tenth of men who are eligible for this option choose surveillance.45 In an observational study of almost 2,000 men with clinically localized prostate cancer, 16 percent were deemed
candidates for active surveillance. Of the group of men who were good candidates, only 9 percent chose surveillance. The rest opted for aggressive treatment.

**For Most Patients, PSA Screening Does More Harm Than Good**

One reason aggressive treatment is chosen so often is that patients are terrified by the diagnosis of cancer and want to be told they have been “cured.” Although this gives patients emotional relief, the claim is overstated. Many of these men would have done well with active surveillance. Moreover, the risks and long-term side effects of treatment can be very consequential.

These statements are based on several prospective, randomized studies. The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) trial randomized 695 men diagnosed with localized prostate cancer to radical prostatectomy or watchful waiting. A small but durable survival benefit was shown for men treated with radical prostatectomy. Not surprisingly, health-related quality of life (HRQOL) was lower in individuals diagnosed with prostate cancer than in population-based, age-matched controls, regardless of the severity of disease. This suggests that simply being diagnosed with prostate cancer, whether treated or not, evokes enough fear and concern to be deleterious to men's overall HRQOL.

A second prospective, controlled trial from Europe randomized 182,000 men to PSA screening or control. It also showed a small reduction in prostate cancer–specific death, but a significant risk of overdiagnosis and treatment. The American Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial found no evidence of a mortality benefit for organized annual screening compared with opportunistic screening, but it did not compare the health outcomes of men who were screened with those who were not screened.

Most notably, a recent meta-analysis of data from 341,342 participants in several high-quality studies examined the value of PSA screening for prostate cancer. It found no reduction in prostate cancer–specific mortality (risk ratio [RR] 1.00, 95% confidence interval [CI] 0.70–1.30) but an increased incidence of harms, mainly due to overdiagnosis and complications of treating what would have otherwise been indolent disease.

Although watchful waiting and active surveillance spare men the worst side effects of aggressive treatment, it does not relieve them of the anxiety of living with cancer. As a result, many live in fear that the disease may someday spread. It is not clear whether the subsequent deterioration of HRQOL that is often seen in this group is due to progressive distress over the diagnosis (a direct consequence of screening), the emergence of cancer-related disease effects, or simply the progressive effects of aging.

The immediate health effects on those who opt for curative treatment are much more dramatic. Many suffer significant sexual dysfunction, urinary symptoms, and other forms of distress. In the only large, prospective, randomized, controlled trial published to date in which the HRQOL of men receiving curative treatment was compared with those who opted for watchful waiting, five-year outcomes revealed significantly more erectile dysfunction (80 percent versus 45 percent) and urinary leakage (49 percent versus 21 percent) in men undergoing prostatectomy, but less urinary obstruction (28 percent versus 44 percent). Other measures, including bowel function, anxiety, depression, well-being, and overall HRQOL, were similar between the two groups after five years. By six to eight years after diagnosis, other psychological domains of HRQOL, such as anxiety and depression, grew worse in those who chose watchful waiting, perhaps in anticipation of the recurring tests, exams, and biopsies required to monitor the condition.
A study at the University of California, San Francisco, Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), has enriched our understanding of temporal changes in HRQOL of men treated for prostate cancer. Enrollees undergoing radical prostatectomy have immediate postoperative declines in disease-specific and general HRQOL, with some recovery in all domains during the first year after treatment. Sexual function continues to improve from the immediate postoperative nadir in the second year, but it rarely returns to the baseline presurgical state. Compared with men treated with external beam radiation therapy, primary androgen deprivation, or active surveillance, sexual function declined most precipitously for those treated with radical prostatectomy, but the prostatectomy group enjoyed the greatest degree of subsequent recovery as well. After all treatment options, recovery of urinary and sexual function generally occurred within two years, with smaller gains in year three. For men treated with radical prostatectomy, urinary function improved over the first year and remained stable in year two. For men treated with radiation therapy, urinary function remained stable, but urinary bother was worse.

As a Result of This Evidence, PSA Screening Is No Longer Recommended by the United States Preventive Services Task Force

In 2012, after reviewing these studies and others, the United States Preventive Services Task Force (USPSTF) recommended against routine PSA screening for prostate cancer. The task force based its position on the determination that more men are physically or psychologically harmed by screening than the small number who potentially benefit.

Despite the USPSTF’s Recommendation, Medicare Is Legally Obliged to Pay for PSA Screening

When the USPSTF released its recommendation against screening, the American Urological Association pushed back, as did its allies in Congress. Rep. Jon Runyan (R-N.J.) and Rep. Joe Baca (D-Calif.), co-chairs of the Congressional Prostate Cancer Task Force, sent a letter to the Secretary of Health and Human Services opposing the USPSTF’s recommendations. Public reactions, including messages posted on social media, were generally critical of the USPSTF recommendations and supported continued PSA cancer screening. Reacting to the criticism, USPSTF co-chair Michael LeFevre qualified that if an individual being screened understands the risks and benefits of PSA screening and makes a personal decision that the small possibility of benefit outweighs the known risk of harm, PSA screening is acceptable.

In May 2013, the American College of Physicians issued two guidance statements on screening for prostate cancer, based on a critical review of existing guidelines:

1. Clinicians should “inform men between the age of 50 and 69 years about the limited potential benefits and substantial harms of screening for prostate cancer.” The guideline further specifies that the decision to use PSA screening should be based on a discussion of the benefits and harms of screening, a patient’s risk for prostate cancer and general health, and patient preferences (“clinicians should not screen for prostate cancer using the prostate-specific antigen test in patients who do not express a clear preference for screening”).
2. Clinicians “should not screen for prostate cancer using the PSA test in average-risk men under the age of 50 years, men over the age of 69 years, or men with a life expectancy of less than 10 to 15 years.”
No organization recommends PSA screening for men older than 75.62 However, many doctors ignore the guidelines, and screening rates remain high.62–63 A recent study showed that 40 percent of men age 75 and older were screened; whether or not a man was screened depended heavily on which primary care physician he saw.64

Despite clinical guidelines and the recommendations of the USPSTF, federal law will continue to require reimbursement for PSA screening until the law is changed. The same is true of similar state laws. In all likelihood, Medicare and other insurers will also continue to pay for the large number of needless biopsies, surgical and nonsurgical extirpations, and the costly side effects and complications they often cause.

**Unintended Consequences**

PSA screening for prostate cancer was envisioned as a low-cost, accurate way to detect a common and potentially deadly form of cancer at a point when definitive treatment could be curative. The rapid uptake and dissemination of the technology triggered a marked increase in the diagnosis and treatment of prostate cancers, many of which would have remained clinically occult or produced indolent disease that would have never have harmed the patient.

The surge in needless biopsies and aggressive treatments that followed undoubtedly cured some cancers that would have otherwise progressed. According to a recent analysis from the USPSTF, if 1,000 men are screened for prostate cancer, one man, at most, will avoid death from prostate cancer (Figure 6.2).59 Among these same 1,000 screened men, the number who experience harms from treatment is much larger: 30 to 40 will lose the ability to control urine leakage or to achieve an erection; two will experience a significant cardiovascular event (i.e., a heart attack); one will have a potentially life-threatening blood clot.59 For every 3,000 men screened for prostate cancer, one will die as a result of surgical treatment.59 The procedures inflicted many cases of psychological and physical harm, including impotence and incontinence. The test also triggered a marked increase in health care spending on prostate cancer testing, treatment, and follow-up. All of these outcomes were unintended consequences of a well-intended test.

PSA cancer screening is costly, and its benefits are scant. The treatments it triggers are even more costly; the diagnosis of cancer is frightening—so much so that the mere knowledge that an individual has the disease degrades his quality of life. The aggressive surgical and radiological treatments used to “cure” cancer patients work in many cases, but they also produce long-term problems. In the years since PSA screening became commonplace, large-scale European and U.S. survival studies have determined that large-scale screening and aggressive treatment of prostate cancer may (or may not) slightly reduce cancer-specific mortality, but it does so at the cost of significant negative effects on the physical and emotional quality of life of large numbers of men. Many would have been spared the costs, discomfort, and complications of aggressive treatment, or the lingering anxiety of living with a diagnosis of cancer, had they not been tested.

For all of these reasons, PSA testing offers an example of a seemingly useful and low-cost test that has been found to produce little more than higher rates of anxiety, treatment-related complications, and health care spending.
Figure 6.2
Benefits and Harms of PSA Screening for Prostate Cancer

1,000 men screened aged 55 to 69 screened every 1 to 4 years for 10 years with a PSA test

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Harms</th>
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<tbody>
<tr>
<td>1,000 men screened.</td>
<td>100-120 false-positive results that may cause anxiety and lead to biopsy (Possible side effects of biopsies include serious infections, pain, and bleeding)</td>
</tr>
<tr>
<td>110 get a prostate cancer diagnosis, and of these men:</td>
<td>- at least 50 will have treatment complications, such as infections, sexual dysfunction, or bladder or bowel control problems</td>
</tr>
<tr>
<td></td>
<td>- 6-4 die from prostate cancer (5 die among men who do not get screened)</td>
</tr>
<tr>
<td></td>
<td>- 6-4 death from prostate cancer is avoided</td>
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</tbody>
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References


Case Study 6: Prostate-Specific Antigen


The Technology

Robotically assisted laparoscopic surgery differs from traditional (i.e., manual) laparoscopic surgery through the coupling of the surgeon's movements to those of a remote-controlled robot. This eliminates tremor. Robotically assisted surgery was pioneered in the 1980s and spread widely over the next two decades into surgical procedures in cardiology, cardiothoracic surgery, general surgery, urology, gynecology, pediatrics, vascular surgery, neurosurgery, and orthopedics.1–3

Rationale

The development of minimally invasive surgery via laparoscopy produced several advantages over open surgery: better visualization (for certain procedures), shorter hospital stays, less postoperative pain, improved cosmesis, lower rates of blood transfusion, and a decreased risk of perioperative infection.4–7 One technical rationale for introduction of the robot was to facilitate challenging surgical tasks, such as suturing with laparoscopic instruments.

Genesis

Initially, robots were utilized to carry out a single task: The PUMA 560 was used to guide a needle for brain biopsy in 1985, and the PROBOT, representing the next generation, was first used in 1988.8–11 In the late 1990s, successful operations for coronary artery bypass grafting and hybrid revascularization were performed in Europe and the United States.12–14 The da Vinci Surgical System first received FDA approval for general intra-abdominal surgery in 2000. The first robotically assisted laparoscopic radical prostatectomies were performed that same year; first in Germany, then France, then the United States.15, 16 A successful cholecystectomy was performed in 2001. Over the rest of the decade, a host of major procedures followed.17–20 The first robotically assisted cadaveric kidney transplant was performed in 2009.21
The development work leading to the da Vinci Surgical System was performed at SRI International, a nonprofit research institute. The work was initially funded by the National Institutes of Health; subsequently, the Defense Advanced Research Projects Agency (DARPA) supported work on the technology. DARPA’s interest centered on the opportunity to use telesurgery and robotics for surgical interventions on the battlefield. The founders of Intuitive Surgical licensed SRI’s technology and went on to further develop prototypes, leading to today’s da Vinci robot.

The Da Vinci Surgical System Dominates the Current Market

The da Vinci Surgical System was not the first approved in the marketplace, but it grew rapidly by buying competitor products. The PUMA 560, PROBOT, and ROBODOC systems predated the development of the da Vinci, and the Computer Motion with AESOP and ZEUS systems rose at roughly the same time as da Vinci. Intuitive Surgical, which makes the da Vinci, came to dominate the market by buying Computer Motion in 2003 and aggressively marketing the da Vinci product thereafter. The merger had the added value of resolving patent infringement lawsuits between the two companies. The deal was financed by equity; Intuitive Surgical issued shares, and final ownership of the merged entity was divided with 68 percent going to Intuitive Surgical shareholders (68-percent equity) and the remainder going to Computer Motion shareholders (32 percent). The deal worked; today, Intuitive Surgical has a near monopoly in the field of robotic surgery.

Early Adoption

Robotic Surgery Expanded Rapidly

Over the past five to seven years, performance of robotic procedures, and the diffusion of robotic technology, has expanded exponentially in both Europe and in the United States. In 2007, approximately 80,000 robotically assisted procedures were performed globally. Three years later, more than 200,000 procedures were performed. Intuitive Surgical’s da Vinci robot is the dominant technology in use today. According to the company, its worldwide installed base as of September 30, 2012, encompasses 2,462 robotic systems. This includes 1,789 systems in the United States, 400 in Europe, and 273 in the rest of the world.

Robotic Assistance Increases the Cost of a Typical Surgical Procedure

The proliferation of this technology has come at substantial cost. The price of a single robotic unit ranges from $1.2 to $2.3 million. Single-use consumables cost $1,300–$2,200 per procedure. Longer operative times involved in using a surgical robot also increase the associated costs per procedure for operating room staff, including an anesthesiologist or nurse anesthetist, scrub nurses, circulating nurses, and technicians. Theoretically, these expenses may be offset to some degree by reduced convalescence, earlier return to work, reductions in hospital length of stay, and minimized analgesic utilization, but the financial benefits of these offsets have not been documented. Overall, robotic assistance increases the cost of a typical surgery by approximately 13 percent (down to about 6 percent if the amortized cost of the robot is excluded).

Interestingly, hospitals do not directly receive increased reimbursement to offset the added cost for robotic surgery versus traditional laparoscopic procedures. Intuitive Surgical
notes this issue in regulatory filings: “A surgical procedure, completed with or without robotic assistance, continues to be assigned to the same MS-DRG . . . both hospitals and physicians receive the same reimbursement amount for their respective services regardless of the actual costs incurred . . . and [reimbursement] is unrelated to the specific products used in that procedure.” In addition, observers have noted that neither Medicare nor many private insurers pay additional fees for robot-assisted interventions. However, hospitals can increase charges for procedures or the diagnoses associated with the robotic system; whether the fees are paid or not is considered proprietary information by hospitals and health plans alike. Also, because Medicare and private insurer reimbursement rates are set based on hospital charges, hospitals can, over time, increase their revenue indirectly. The most tangible benefit of acquiring a robotic system, given the fact that hospitals function in a high fixed-cost environment, is the additional surgeons—and surgical volume—that they attract.

Economics aside, hospitals in competitive markets often acquire cutting-edge technology to differentiate themselves, attract surgeons and surgical case loads, and signal their advanced competence. At least one hospital executive has noted that competitive pressure played in his decision to acquire a robotic surgical system.

The Impact of Adoption Is Most Dramatic in Prostatectomy Procedures
The transition from open surgery to laparoscopy to robotic-assisted laparoscopic procedures has been most striking for surgical removal of the prostate. Following the first robotically assisted radical prostatectomy in 2000, uptake was slow until about 2005, when adaptation accelerated at a rapid rate. Although the technology was introduced into clinical practice only 12 years ago (FDA regulatory clearance for use in prostatectomy procedures was granted in May 2001) and did not begin to widely proliferate before 2005, it has transformed how radical prostatectomies are performed. Today, approximately 80 percent of all radical prostatectomies in the United States are performed with robotic assistance.

As robotic capabilities increased, not only did the percentage of surgical candidates undergoing prostatectomy by robotic procedure increase; so did the overall number of surgical prostatectomies. Since 2005, the number of prostatectomies among both older (>65 years old) and younger (<65 years old) U.S. men has increased by 60 percent.

Growing Reliance on Surgical Treatment of Prostate Cancer Is Linked to the Growing Use of Robotic Technology
Today, far more men diagnosed with prostate cancer opt to undergo prostatectomy, compared with a few years ago. Although some may view this development as a sign of progress, it is not necessarily positive, since there is ample evidence that other approaches, including radiation therapy and active surveillance (“watchful waiting”), may yield equivalent outcomes at lower cost (and, in the case of active surveillance, fewer side effects).

The striking increase in operative treatment is not explained by changes in the underlying incidence or severity of disease. Instead, it appears to be related to the growing availability of robotic surgical technology. Studies of hospital and local health care market practices strongly suggest that the recent increase in surgical treatment of prostate cancer is both geographically and temporally related to acquisition of robotic surgical systems (see “Subsequent Use,” below).

More-aggressive treatment is not necessarily better for patients. Recently, an analysis of linked Surveillance, Epidemiology, and End Results—Medicare (SEER-Medicare) claims
demonstrated that use of advanced technologies, such as robots, has increased dramatically, even among those men who are not good candidates for surgery, such as those with low-risk prostate cancer, and men at high risk of noncancer mortality. In these groups, prostate surgery is generally regarded as equivocal (i.e., low-risk prostate cancer) or inappropriate (i.e., men at high risk of surgical complications or noncancer mortality). In these groups, current guidelines advise against screening for and treatment of prostate cancer.57, 58

Subsequent Use

Acquisition of Robots Has Boosted Radical Prostatectomy Rates in Hospitals That Get Them

Data from the Healthcare Cost and Utilization Project (a family of databases comprising multistate, inpatient, and outpatient discharge records on insured and uninsured patients) suggest that diffusion of the technology produced dramatic changes in hospital markets. Early in the robotic diffusion period (2001–2005), hospitals that acquired a surgical robot increased their prostatectomy case volume by an average of 30.1 cases annually (95% confidence interval [CI] 23.37, 36.4), compared with a change in volume of –4.9 cases annually (–7.2, –2.7) in hospitals not acquiring a robot during the same time period.53 At the level of hospital referral regions (HRRs), radical prostatectomy rates increased in regions that acquired robots, compared to HRRs where robotic system were not acquired (Figure 7.1). For example, an HRR gaining

Figure 7.1
Mean Change in HRR Number of Radical Prostatectomy Procedures Following Robot Acquisition, Controlling for Baseline HRR Volume and Herfindahl Index

three robots between 2001 and 2005 saw an estimated annual increase of 106.6 radical prostatectomy cases per year, controlling for baseline HRR volume and Herfindahl index (a measure of market concentration used by the U.S. Department of Justice when considering horizontal mergers).59

Hospitals with Robots Attract Cases
Early on, it is likely that most of the growth in case volume of HRRs with robots was drawn from HRRs where no robot was installed. The latter saw a decrease in case volume by an estimated 41.2 cases annually.53 Therefore, during the early period of robotic technology adoption, the overall rate of surgical intervention for radical prostatectomy remained relatively stable. The primary effect of robots appeared to be attracting surgical cases to the hospitals that acquired them.

After 2005, Robots Triggered Market Consolidation and Intensification
Analyses conducted in the post-2005 era, when use of robotic surgery surged, paint a different picture. At this phase of diffusion, the effects of the technology on health care practice—and, therefore, spending—grew more profound. For example, a population-based analysis of radical prostatectomy procedures in New York, New Jersey, and Pennsylvania demonstrated that the total number of radical prostatectomy procedures grew substantially, from 8,115 in 2000 to 10,241 in 2009, a 26-percent increase.54 Most of the increase was noted at high-volume hospitals that acquired a robotic surgical system. Interestingly, while the total number of cases grew by over 2,000 procedures annually, the number of hospitals performing this surgical procedure fell by 37 percent, from 390 hospitals in 2000 to 244 in 2009 (Figure 7.2). By 2009, slightly more than 35 percent of hospitals—those with a surgical robot—performed 85 percent of all radical prostatectomies, indicating that robots were triggering both market consolidation and intensification.54

Robots Also Influenced Surgical Training and Practice
Based on case log data for initial board certification and recertification, a growing number of urologists stopped doing open procedures and only performed robot-assisted radical prostatectomies. In 2004, 13 out of 427 urologists (3%) performed only robotically assisted radical prostatectomies; by 2010, there was a sixfold increase (95 out of 500 [19%]).55 Similarly, among urologists undergoing initial certification or recertification, the proportion performing both open and robotic procedures increased dramatically, from 18 out of 427 (4%) in 2004 to 153 out of 500 in 2010 (31%). By 2010, half of practicing urologists used the robotic technique in either all or some of their cases; the other half continued to perform only open prostatectomies. The increased reliance on robots has been noted among urologists undergoing initial board certification, as well as those undergoing recertification.55

Robot-Assisted Prostatectomy Affects Diagnostic Procedures, Disparities, and Inappropriate Use
Other effects on patterns of care—some concerning—were noted during this transition. For example, after controlling for preoperative cancer risk group, an analysis of SEER data found that men undergoing robot-assisted prostatectomy were less likely to undergo pelvic lymph node dissection.60 Node sampling is important because it provides prognostic information in men with intermediate or high-risk cancer. Other investigators have noted economic dispari-
Figure 7.2
Trends in Radical Prostatectomy Procedure Volume and Number of Hospitals Performing the Procedure in New York, New Jersey, and Pennsylvania54

ties in the location of hospitals acquiring robotic systems. Hospitals situated in areas associated with lower-income and higher-minority populations are less likely to acquire robotic systems. Thus, while these hospitals may be offering comparable quality of care, they may be losing revenue-generating urological cases to hospitals that can afford to purchase a surgical robot. Consistent with the market consolidation hypothesis, the distance traveled by patients undergoing robot-assisted radical prostatectomy has recently increased. Finally, a more recent analysis of SEER cancer registry data linked to Medicare claims suggests that use of robotic technology is growing rapidly among patient groups that are least likely to benefit from the technology and may even be harmed: men with low-risk prostate cancer and those at high risk of noncancer mortality.

Impact on Health and Costs

Despite the quick uptake and rapid proliferation of surgical robots, there is no evidence, based on properly designed randomized controlled trials, that robotically assisted radical prostatectomies produce better outcomes or reduced side effects relative to manual (open) radical prostatectomy. Several prospective, nonrandomized trials have been performed; generally, these studies have found that patients who undergo robotically assisted surgery have a somewhat more-rapid convalescence, shorter hospital stays, and less blood loss than conventional cases. Other studies, which produced less-reliable evidence because they used retrospectively compared case series or historical series as controls, have reported similar findings. Recently, the Health Technology Assessment Program of the Washington State Healthcare Authority published an assessment of the robotic technology. After analyzing the available data, the program concluded that the level of evidence supporting use of the technology was moderate and, therefore, that the service would be covered. However, it did so with the proviso that no additional payments be made beyond what the state would pay for the traditional procedure.

The most robust comparison of outcomes between robotic and open radical prostatectomy performed to date was a SEER-Medicare analysis that used propensity score adjustment before comparing the outcomes of the group receiving robotic surgery versus those treated with open (traditional surgery) extirpation. As was noted by earlier assessments, use of the robotic approach was associated with shorter lengths of stay, lower rates of blood transfusion, and lower postoperative respiratory complications. However, the robotic approach was also associated with more-frequent surgical complications, including urinary incontinence, genitourinary complications, and erectile dysfunction. Given adequate knowledge of these trade-offs, many men might not opt for robotic surgery or might select a nonsurgical option, such as watchful waiting, radiation therapy, or implants.

Hospitals Cite Robotic Surgery in Marketing

Despite the lack of evidence that robotic surgery is superior to open surgical approaches, hospitals frequently tout the advantages of robotic surgery. Hospital websites often use images and text taken directly from the manufacturers of robotic systems and promise improved perioperative outcomes, decreased complications, reduced operative time, shorter recovery, less scarring, reduced risk for infection, and less pain. Some of these advertisements use high-tech or emotional language, such as “state-of-the-art,” “cutting edge,” “you owe it to yourself,” and “loved one.” Marketing claims include higher lymph node yield, improved cancer out-
comes, and “ideal treatment.”77, 78 None of these claims is substantiated by rigorous evidence; some, such as node sampling, are contradicted by the available evidence.60

The training given to surgeons who are beginning to use a robot has not been studied intensively, but it appears to be highly variable. Recently, Intuitive Surgical was the defendant in a case in Washington State (Estate of Fred E. Taylor v. Intuitive Surgical Inc., 09-2-03136-5). The plaintiffs focused on Intuitive’s recommendation that a one-day session at the company headquarters, followed by two supervised robotic surgeries, is sufficient to prepare surgeons to perform robotic procedures. The jury found for Intuitive Surgical, so no claims were paid.79

An important question in evaluating any new technology is whether or not it produces better outcomes than the technologies it is replacing. Therefore, it is reasonable to ask whether the evidence compiled to date indicates that robotic surgery is superior to open surgery for treating cancer of the prostate. Unfortunately, no rigorously randomized controlled trials comparing open and robot-assisted radical prostatectomy have been performed. Most studies that have examined the effectiveness of robotic surgery employ observational designs that are prone to bias (i.e., patients are selected to one group or the other based on characteristics that may independently influence their outcome). Therefore, these studies are generally considered to represent a lower level of evidence.

A Medical “Arms Race”

Adoption and diffusion of robotic surgical technology has been rapid and extensive. Although there is scant evidence that the technology improves short-term surgical outcomes—and some evidence that it may create problems as well—the technology has transformed the landscape of prostate cancer treatment in the United States. When early adopters of robotic surgical systems began advertising that they had the technology and started drawing cases from non-adopting hospitals, it set off a “medical arms race” between competing hospitals and health care systems.43 Soon, hospitals scrambled to acquire the technology in order to retain or attract urologic surgeons and the cases they perform. Although third-party payments for the technique are generally similar to those associated with conventional open surgery, hospitals that adopted the technology have dramatically boosted their surgical caseloads relative to hospitals that did not. Thus, the technology has driven health care spending higher without making an appreciable impact on the health or long-term prognosis of patients treated with robotically assisted surgery.

Although there is no evidence that robotically assisted surgery is superior to alternative approaches, including conventional open surgery, radiation therapy, and watchful waiting, rates of surgical prostatectomy are up, and the large majority of prostate removal surgeries use robotic technology. More follow-up data are needed to fully understand how this technology affects the treatment and long-term outcomes of men with prostate cancer.

Robotic surgery is only one example of the medical arms race. Other costly technologies, such as the even costlier proton beam therapy, have also emerged in recent years. Hospitals that acquire these extraordinarily expensive machines (more than $180 million each) hope that the allure of the technology and the prestige it confers will attract patients to their facility.83 Similar to claims made in support of robotic surgery, proponents of proton beam therapy claim that the technology offers greater precision, improved efficacy, less damage to healthy tissue, and fewer side effects than older or less-costly techniques.80 However, there is no evidence that
proton beam therapy offers victims of prostate cancer (or many other cancers) better outcomes than that provided by less expensive conventional (photon) radiation therapy.84

Medical “arms race” technologies such as these have done little or nothing to improve the health of men with prostate cancer. They have, however, increased the intensity of treatment offered to middle-aged and elderly men with this common, frequently indolent, and, by many measures, already overtreated condition. And because there is substantial evidence that aggressive treatment may not only be costly but also harmful, it may offer little value to those whom these technologies were designed to help.81, 82

References


Case Study 7: Robotic Surgery


CASE STUDY 8

Telemedicine

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The Concept

Telemedicine has its roots in Europe. In 1905, Dutch physician and inventor Willem Einthoven (1860–1927) demonstrated the feasibility of transmitting and receiving cardiograms over telephone lines. He referred to this as the “tele-cardiogram.” In the United States and Canada, several projects with different applications were conducted between 1948 and the early 1970s, involving psychiatry and single-specialty and multispecialty clinics, using various terms with the prefix tele- (meaning “distance”). Kenneth Bird popularized the term “telemedicine” in the 1970s.¹

Telemedicine represents a modality in health care delivery that relies on information and communication technology (ICT). Types of health care services include primary and specialty medical care, patient monitoring, consumer health information, and medical education.² The way the services are delivered generally entails one of two basic modes that largely differ in terms of the timing of information acquisition, transmission, and response between the parties that send and receive the information.

Store-and-Forward (Asynchronous) Mode

This mode involves collection of data (including presenting symptoms, medical history, lab tests, and images), transmission, retrieval, and response. Clinical data are acquired from the patient at the remote site and transmitted to the consultant (typically in a medical center), who reviews and interprets the data at a time convenient to her or him and subsequently renders an opinion about diagnosis and/or treatment. The two-way transmission of information is “asynchronous” because it does not require simultaneous availability of the patient and health care consultant during the encounter.³ ⁴ It is often used in radiology, dermatology, and pathology—specialties that rely on images for diagnosis and treatment. In the case of radiology and pathology, contact with the patient is not normally required. A somewhat similar application is observed in the remote monitoring and management of chronic illnesses, such as heart disease, diabetes, and chronic obstructive pulmonary disease. In this case, patients transmit hemodynamic, anthropomorphic, or laboratory data (e.g., blood pressure, heart rate, weight, blood glucose measurements), collected manually or electronically, to a clinic or call center staffed with nurses and specialists. Feedback may or may not be provided in real time.⁴

¹ Acknowledgments: To Rashid L. Bashshur, Ph.D., for his editorial support.
Real-Time (Synchronous) Mode

In this mode, patient and provider interact in real time via ICT. Hence, the encounter is synchronous (occurring at the same time but at different locations). The processing and interpretation of data occur in real time and require the simultaneous availability of the patient (often attended to by the local health care provider) and the remote consultant (typically located at a medical center), who provides diagnosis and treatment recommendations. This mode is used most commonly to deliver specialty care in various areas, as well as primary and critical care.1, 4

Depending on the type of service being delivered, telemedicine has been used to connect such parties as medical centers, clinics, independent providers, monitoring centers, and patients. It employs a range of technologies, including videoconferencing, Internet links, and mobile devices for information exchange between provider and client.1

Rationale

The goal of telemedicine is to extend the reach of health care providers to serve patients beyond the constraints of geography and time. Beneficiaries have included remote, confined, or underserved populations. Primary objectives include the following:1–3, 5

1. to promote equity of access to care for those who are geographically, financially, logistically, and/or culturally challenged in the receipt of care
2. to enhance the efficiency and effectiveness of health care systems by relying on rational triage of patients at the point of need, providing care at the appropriate place and time, and relying on established protocols
3. to reduce opportunity cost for patients, as well as itinerant providers, by obviating the need for unnecessary travel
4. to contain health care costs by reducing unnecessary duplication of diagnostic testing; reducing unnecessary hospitalization and emergency room visits; and fostering information-sharing among health care providers, institutions, and patients.

The case for telemedicine is even more compelling in the context of health care reform.6 Bashshur and Shannon, writing on behalf of a diverse group of health care academicians, providers, researchers, and industry representatives across the United States with expertise in telemedicine, provide a strong case for the necessity of telemedicine in effective health care reform.5

Development

Although the concept of remotely guided health care is not new, it has dramatically evolved with advances in technology since the 19th century. In History of Telemedicine: Evolution, Context, and Transformation (2009), Bashshur and Shannon deliver a comprehensive account of the history of telemedicine, from its genesis in ancient societies to its adoption by the modern health care system.5

Telegraphy, an early form of telemedicine, was used to transmit casualty lists and facilitate ordering medical supplies on the battlefield during the Civil War. The invention of the
telephone in 1876 and the subsequent development of telephonic networks would later enable more-rapid, bi-directional voice and data transmission for medical diagnosis and treatment, such as amplified stethoscope sounds, electrocardiograms, and electroencephalograms. At the end of the 19th century, radio technology was used to extend medical care to seafarers.\textsuperscript{1, 3} Dutch physician and physiologist Willem Einthoven, considered to be the first authentic telemedicine pioneer, used the newly developed galvanometer to measure electrical charges from the heart and transmit them via telephone wire as the first “tele-cardiogram” in 1905.\textsuperscript{1}

Organized telemedicine systems started in the 1960s and 1970s and relied on closed-circuit television, microwave transmission, and satellite communications:

- In 1964, the U.S. National Institute for Mental Health (NIMH) funded the creation of a two-way closed-circuit television system between the Nebraska Psychiatric Institute in Omaha and the Norfolk State mental hospital 112 miles away. The system was used to provide interactive medical consultations and education between specialists and general practitioners.\textsuperscript{7}
- In 1967, Kenneth T. Bird created an interactive television system that linked Boston’s Logan Airport and Massachusetts General Hospital. The system used direct microwave transmission to provide 24-hour medical consultation to over 1,000 airline travelers and employees.\textsuperscript{8}

The National Aeronautics and Space Administration (NASA), which had been using telemedicine to meet the health care needs of astronauts on space flight missions, played an instrumental role in the development and application of these technologies. NASA’s early telemedicine systems were developed to collect basic physiologic data to study the effects of space travel on the human body. In the 1970s, NASA began applying its resources and experience to several terrestrial health care projects:\textsuperscript{9}

- In 1971, NASA’s Applied Technology Satellite-1 (ATS-1) was used by the U.S. National Library of Medicine’s Lister Hill National Center for Biomedical Communication to study the reliability of providing satellite-mediated video consultation to 26 Alaskan village sites.\textsuperscript{10} This was the first part of a multi-stage project that ultimately linked remote villages, field service unit hospitals, and medical centers via a satellite voice network that was credited with improving the efficiency of medical care and saving lives in the region. Because of the success of this project, Alaska dedicated $5 million toward the purchase and installation of satellite earth stations in 200 remote villages, linking each of them with regional hospitals and the Alaska Native Medical Center.\textsuperscript{1}
- In 1972, NASA began the Space Technology Applied to Rural Papago Advanced Health Care (STARPAHC) program to test a terrestrial-based telemedicine system for its manned space program. The test site was the Papago (now Tohono O’odham) reservation. In addition to fixed locations on the reservation near Tucson and Phoenix, Arizona, a specially designed and fully equipped mobile health unit (MHU) traveled on a scheduled route to serve sparsely populated destinations on the reservation. The MHU was linked via two-way microwave transmission (including redundant narrow- and broadband) to physician consultants at the small Indian Health Service (IHS) hospital in Sells on the reservation and a referral IHS diagnostic center in Phoenix. Fully sponsored by NASA, the project was implemented jointly by NASA, the Indian Health Service, and Lockheed Missile and
Space Company. The STARPAHC project was operational for three to four years and was gradually phased out by NASA.1, 11

- In 1977, satellite technology was adopted internationally when Canada's Memorial University of Newfoundland employed the joint Canadian/U.S. Hermes satellite to deliver distance education and medical care across the province.12

The 1960s and 1970s laid the conceptual foundations for modern telemedicine. Much of the efforts were supported by federal agencies, including NASA; the U.S. Department of Health, Education, and Welfare (DHEW); and the U.S. National Science Foundation, especially the seven exploratory projects funded by the Health Care Technology Division of DHEW. There were several limitations in these early telemedicine projects, including expensive, bulky, and unreliable equipment; restrictions in licensed public use frequencies; limited acceptance by the medical profession; design flaws; and a lack of business plans that would secure long-term sustainability. The issue of reimbursement for telemedicine providers was not relevant at this time; demonstration projects were terminated when public funding expired. Telemedicine did not take off until the 1990s and 2000s, when advances in computers and telecommunications and the dropping cost of information technology enabled its adoption in a growing number of clinical practices. The recognition that telemedicine had the potential to help address problems in health care delivery (e.g., limited access, rising costs, and variations in quality) also encouraged its adoption.

**Early Adoption**

In the 1980s, most of the activity was focused on teleradiology, the quintessential form of “store-and-forward” telemedicine. The first teleradiology systems were characterized by inefficiency, poor quality, limited scalability, and high cost. Photos or videos of hard copy radiology films were digitized for image transfer, enabling radiologists outside the hospital to provide remote and after-hours readings. Despite the potential benefits of these systems, the secondary digitization process was cumbersome and time-consuming because images had to be handled one at a time. The degradation of image quality during transmission was another concern. Other obstacles included the expense of the equipment (e.g., computer, digital imaging and data transmission systems) and the proprietary nature of teleradiography software.9

By the 1990s and 2000s, the rise of the Internet and the rapid incorporation of picture archiving and communications systems (PACS) into radiology transformed the field.9 PACS are medical imaging systems that allow storage, retrieval, transmission, and archiving of digital images. They consist of an imaging modality, a secure network for data transmission, computer-based workstations for image interpretation, and archives for image storage and retrieval.13 The digital image communication in medicine (DICOM) standard was established by the American College of Radiology and the National Electrical Manufacturing Association, helping to ensure the quality of images transferred. For an in-depth review of the history and key issues pertaining to teleradiology, see Joseph Gitlin’s chapter in *Telemedicine: Theory and Practice*.14

Some of the first PACS research and development projects were funded by the U.S. Army in the early to mid-1980s. One of these was the Installation Site for Digital Imaging Network and Picture Archiving and Communication System (DIN/PACS) project, which was led by
the MITRE Corporation in collaboration with Philips Medical Systems and AT&T and rolled out at two academic universities.\textsuperscript{15} Over the next decade, the National Institutes of Health funded several large-scale PACS research projects at the University of California, Los Angeles (UCLA), which ultimately led to introduction of PACS into clinical care at that institution. Expertise gained in the UCLA projects was used to develop a hospital-integrated PACS at the University of California, San Francisco (UCSF), Medical Center in 1996. Funding for the latter project was provided by the National Library of Medicine, the Army Medical Research and Materiel Command, the National Cancer Institute, the California Cancer Research Program, Pacific Bell, and UCSF.\textsuperscript{16}

The development of compression algorithms opened the door for the transmission of large amounts of data over limited bandwidth, which improved digital image capture and data transmission. PACS systems produced rapid improvements in teleradiology’s efficiency, quality, scalability, and cost. Simultaneously, the development of newer digital imaging techniques (e.g., computed tomography and ultrasound) increased the opportunities for teleradiology. The incorporation of PACS into clinical practice enabled the existing supply of radiologists to meet this demand by providing interpretations remotely without the earlier concerns about excessive cost and the degradation of image quality.\textsuperscript{9}

In addition to the store-and-forward systems used by teleradiology, real-time telemedicine applications began to diffuse rather rapidly. For example, telepsychiatry—the delivery of psychiatric services using live interactive videoconferencing—emerged as an alternative to face-to-face treatment.\textsuperscript{17} The development of computer-based systems, videoconferencing, mobile technology, and digital communications expanded opportunities for patients to receive mental health treatment from providers located elsewhere. Similar technology is being employed by neurologists to manage both acute and chronic neurologic conditions, such as stroke, epilepsy, and movement disorders, particularly in patients who live in rural areas and have limited ability to travel.\textsuperscript{18}

Subsequent Use

Expansion to Clinical and Academic Environments

Once the pioneer projects of the 1960s showed that the concept was feasible and advances in technology made it practical, telemedicine began to expand in both clinical and academic arenas. A 2002 survey of teleconsultation activity (excluding teleradiology) in the United States reported that over 85,000 teleconsultations were performed by more than 200 programs in 30 specialties.\textsuperscript{19} The most represented medical fields were mental health, pediatrics, dermatology, cardiology, and orthopedics.\textsuperscript{19} The literature on telemedicine grew as well. Between 1964 and 2003, the number of papers on telemedicine indexed on MEDLINE increased from a few each year to 700–800 annually, with the greatest output occurring during the 1990s.\textsuperscript{20} Two peer-reviewed journals dedicated to telemedicine were launched: \textit{Telemedicine and E-Health} and the \textit{Journal of Telemedicine and Telecare}.\textsuperscript{21} The American Telemedicine Association (ATA) was founded in 1993 as a nonprofit organization composed of individuals, health care institutions, companies, and other organizations dedicated to promoting telemedicine throughout the world.\textsuperscript{22}
The Affordable Care Act Encourages Telemedicine to Expand Access
More recently, telemedicine was embraced by the drafters of the Affordable Care Act of 2009 (ACA) as a promising means of expanding access to health care and care coordination across settings. The ACA directs the Center for Medicare and Medicaid Innovation (CMMI) to study ways to improve the use of telemedicine to treat behavioral problems and stroke in the IHS as part of a broader goal to promote cost-effective care. CMMI is also encouraged to incorporate such technologies as patient-based remote monitoring systems into delivery models to improve care coordination.6, 18

Advances in Telecommunications and Computer Technology Facilitate Adoption
By far the most important factor facilitating the adoption and dissemination of telemedicine has been the rapid advances in telecommunications and computer technology that have occurred over the last 10–20 years. In particular, the switch from analog to digital technology and the decreasing cost of information transmission have played a major role in fueling the expansion of telemedicine. In addition, the creation of the Internet, computer networks, and web-based applications have enabled a variety of real-time telemedicine applications that would have been technically impossible a generation ago.3, 9 However, as the barriers of technology have fallen by the wayside, new barriers have emerged to limit the widespread adoption and dissemination of telemedicine.

Barriers
Regulatory Barriers
Perhaps the most formidable barrier to expanding telemedicine today is the current system of medical licensure regulation. In our federal system of government, the states have the authority to ensure the quality of medical care provided to their residents. One means by which they do this is by regulating medical licensure. State-level regulation worked well for many years when medical care was almost exclusively delivered on a face-to-face basis. However, it presents challenges to physicians who want to practice telemedicine across state borders.

Currently, all state medical licensing boards require that a physician engaging in telemedicine hold a medical license in the state where the patient is located.23 There is no reciprocity between states to allow a physician licensed in one state to practice telemedicine in another, despite the existence of national board examinations, national specialty certification, a national malpractice data bank, and the similar medical licensing requirements between the states.24

In 1994, the American College of Radiology (ACR) published the ACR Standards for Teleradiology. The standards mirror existing state laws by asserting that physicians providing official interpretations through teleradiology should maintain licensure in both the initiating and receiving states. Furthermore, the ACR standards stipulated that physicians also hold staff hospital staff credentials at the site of the patient encounter.9 Some states go even further, requiring the practitioner to obtain written consent from the patient to participate in telemedicine, to have a medical staff person present with the patient, and to incorporate face-to-face visits into the treatment plan.17 Presumably, the rationale for these policies is protection of patient safety. But they are sufficiently burdensome to make telemedicine infeasible in most instances. Also, there are no data to support the need for these requirements or to prove that their addition provides the desired margin of safety.
The need for physicians to obtain licensure across multiple states—and even credentials at each individual hospital—serves as a major barrier to the expansion of telemedicine. As a result, few physicians are legally credentialed to provide telemedical care to patients in remote or underserved areas. Until a solution to this problem is found, the potential benefits of telemedicine will not be fully realized, despite needy patients, willing providers, and the requisite enabling technology. The consequences of limiting expansion of telemedicine will become increasingly apparent when ACA implementation increases the number of insured patients in 2014 and thereafter.

In 2011, the ATA proposed four potential strategies to reduce the regulatory barriers that impede the practice and expansion of telemedicine:24

1. Create a federal medical licensure and regulation system (modeled after that used by the Federal Aviation Administration for licensure of civilian airline pilots).
2. Maintain a state-level medical licensure and regulation system without the requirement that practitioners of telemedicine be licensed in the state in which the patient resides. Instead, the state in which the provider is located would have regulatory authority over the licensing and activities of the provider.
3. Grant functional licensure, which would supersede state requirements, in defined circumstances. An example of this is the Veterans E-Health and Telemedicine Support (VETS) Act (H.R. 2001), a bill introduced in Congress in May 2013. This act would provide an exemption from the need to obtain multiple state licenses to U.S. Department of Veterans Affairs health care providers.25
4. Create a system of mutual recognition and portability of medical licenses between states (modeled after that used for issuing drivers licenses).

Legislation designed to foster a voluntary national medical licensure system is currently being drafted by Sen. Tom Udall of New Mexico, who represents a state with substantial rural and frontier areas. The proposed system would provide a uniform set of standards and application process for national medical licensure and create a comprehensive data exchange system for primary source verification of credentials. Physicians holding a valid state medical license would be eligible to apply for a national license. The combination of the two would enable a physician to practice telemedicine across state lines.26

Financial Barriers
Expansion of telemedicine is hindered by financial barriers as well. Chief among these is the still-substantial cost of the technology and insufficient reimbursement for telemedicine services. For example, restrictive Medicare reimbursement policies leave substantial gaps in coverage. Medicare only reimburses for telemedicine services provided to patients living in a Health Provider Shortage Area or a county outside of a metropolitan statistical area (MSA). Given that nearly 80 percent of Medicare beneficiaries live within one of the 1,092 MSAs (yet still have poor access to care), this policy significantly limits the number of patients who might otherwise benefit from telemedicine services.

Furthermore, reimbursement is contingent upon the patient being physically present in a “medical facility” (e.g., a provider’s office, hospital, or rural health clinic). Home consultations do not qualify. This provision preempts one of the principal benefits of telemedicine: providing expert care to mobility-impaired patients and those who live in remote settings.27
Medicaid imposes additional restrictions. Because Medicaid is a joint federal and state program, the states can decide whether to cover telemedicine services. States may choose which services to cover, where in the state telemedicine can be provided, what types of providers are covered, how much providers will be reimbursed, and other terms. Only ten states have legislation authorizing Medicaid coverage for telemedicine, mostly interactive video consultations.

Private health plans have their own restrictions. Currently, there is no widely accepted standard among private plans for reimbursing telemedicine providers, so their approaches are highly variable. Only 19 states have legislation mandating coverage of telemedicine services by private payers. Taken together, the restrictive reimbursement policies by government and commercial payers sharply limit the viability of telemedicine services, inhibiting the pace and extent of adoption.

The one exception to the slow pace of adoption is teleradiology. Because remote viewing of medical images—a core aspect of teleradiology—is not considered “telemedicine” by the Centers for Medicare & Medicaid Services (CMS), teleradiology services are quickly and consistently reimbursed. Thus, the use of PACS and other aspects of teleradiology is widespread.

Because reimbursement is so variable and is often lower than care provided in a typical face-to-face encounter, the cost of acquiring the technology remains a barrier as well. Prices are much lower than a decade ago, but they are still substantial. Miller et al. reported that the costs for purchasing a basic electronic medical record system—a prerequisite to an efficient telemedicine capability—are approximately $44,000 per physician for initial startup and $8,500 per physician per year for maintenance, respectively. Regions of the United States that lack the infrastructure or funding to acquire this technology face particular challenges, leading to geographical and socioeconomic disparities in access to telemedicine services.

Provider Reluctance
The third major barrier is the lack of interest on the part of many health care providers to incorporate telemedicine into their practice. Providers may be reluctant to invest the time and resources into learning and staying updated on new technology and telemedicine systems. Others have cited concerns about disrupting the traditional physician-patient relationship through the interposition of technology.

Medico-Legal Concerns
Telemedicine services, which may consist of consultations through video, email, or other electronic media, create scenarios that challenge existing patient privacy and malpractice laws. In telepsychiatry, psychiatrists providing mental health assessments and treatment to patients through videoconferencing systems must ensure that their systems meet the requirements of the Health Insurance Portability and Accountability Act (HIPAA) and federal and state privacy statutes. The ways in which current legal criteria apply to telemedicine consultations using electronic media are unclear, including professional expectations, practice standards, and potential liabilities associated with use of the technology.

Uncertain Benefits
Whether policymakers, private investors, and health care providers will push for the expansion of telemedicine depends in large part on the compilation of evidence of its clinical and economic value. This is discussed more fully in the next section.
Cost and Health Impact

Telemedicine was created to expand access to care, improve quality of services provided to rural and underserved populations, promote health care equity, increase work efficiency, reduce health care costs, and improve inter-professional communications and information-sharing within the health care system. However, the extent to which these benefits have been documented in the medical literature is limited. One reason is that the adoption of telemedicine into clinical practice—and, therefore, the study of its clinical and economic outcomes—is relatively new. This creates a catch-22: Although telemedicine is technically feasible, its impact on costs and quality of care has not been demonstrated in a compelling way. But without adequate dissemination to conduct the evaluation, it is impossible to prove its potential impact.

Second, the heterogeneity of the interventions makes it challenging to draw general conclusions about the overall effectiveness of telemedicine. Individual programs have demonstrated positive outcomes among patients, families, health care providers, and the health care system, including increased access to health care services, cost-effectiveness, enhanced educational opportunities, improved health outcomes, better quality of care, and enhanced social support. However, when these studies are merged in systematic reviews and meta-analyses, the results are mixed.

For example, Currell et al. conducted a systematic review of studies comparing telemedicine programs with face-to-face patient care. Seven studies involving 800 patients were included. Included telemedicine programs used at least two communication media interactively, and the majority involved home care or patient self-monitoring for chronic disease. The review demonstrated feasibility and acceptability of the programs; however, the impact of telemedicine on clinical outcomes, including safety, was unclear. Furthermore, there was insufficient information to determine the cost-effectiveness of the interventions. In another systematic review, Whitten et al. concluded that there was little published evidence to confirm whether telemedicine is a cost-effective alternative to standard health care delivery.

Notwithstanding these studies, there is also evidence of the effectiveness of telemedicine in the medical literature. As one example, McLean et al. conducted a meta-analysis of 21 randomized controlled trials of telemedicine interventions for pediatric and adult asthma management. Telemedicine asthma interventions used a range of technologies, including telephone, video conferencing, Internet, text messaging, and other networked systems. They found no difference in patient-reported quality of life and number of emergency department visits when comparing patients who were served by telemedicine and those who were not. However, there was a reduction in the rate of hospitalizations among patients who received the intervention.

A second example is a longitudinal analysis of the business value of implementing and integrating electronic medical records, radiology information systems, and PACS at a regional medical center. Outcomes of financial revenues, operating lead times, and customer satisfaction were examined. In the 12 months after information technology implementation, there was a 20- to 40-percent increase in revenues related to improvements in billing, an 80-percent reduction in turnaround time for generating final radiology reports (a marker of work efficiency), and a statistically significant increase in satisfaction among referring physicians.

It would be premature to make sweeping generalizations about the utility of telemedicine from these reviews. Craig and Patterson suggest that the outcomes of telemedicine programs should be evaluated on an individual basis. They argue that because each telemedicine program is designed to serve a specific purpose within a defined context, the relative importance
of desired outcomes (feasibility, acceptability, cost, effectiveness, safety, and sustainability) will differ from program to program. In addition, they suggest that studies comparing telemedicine interventions with face-to-face patient care may not be relevant or appropriate if the intent of the intervention is not to replace face-to-face encounters or specialist referrals, but rather to enable provision of care in settings where conventional services are highly limited or nonexistent.3

It is ironic that telemedicine programs are expected to show superiority over face-to-face encounters with clinicians, while the much larger and more powerful pharmaceutical industry need only show that a new drug is relatively safe and better than placebo to gain regulatory approval. If new drugs were required to show superiority over existing products on the market, few could meet that standard.

Prospective research on the impact of telemedicine, particularly in austere settings that currently have inadequate access to care, could resolve this question. Performing such studies would fill a major gap in the telemedicine literature and encourage greater stakeholder support for this promising technology.21 Until such evidence is generated, the expansion of telemedicine is likely to be slow.

In 1996, the Institute of Medicine (IOM) released the report Telemedicine: A Guide to Assessing Telecommunications for Health Care.38 In that report, the IOM Committee on Evaluating Clinical Applications of Telemedicine offered the following observation (p. 208):

Telemedicine is similar in most respects to other technologies for which better evidence of effectiveness is also being demanded. Telemedicine, however, has some special characteristics—shared with information technologies generally—that warrant particular notice from evaluators and decision makers. Most notably, telemedicine is not a single technology or a discrete set of related technologies; it is, rather, a large and very heterogeneous collection of clinical practices, technologies, and organizational arrangements. In addition, widespread adoption of effective telemedicine applications depends on a complex, broadly distributed technical and human infrastructure that is only partly in place and is being profoundly affected by rapid changes in health care, information, and communications system.

Sixteen years later, the IOM revisited telemedicine and “telehealth” in a major workshop.39 Sponsored by the Health Resources and Services Administration (HRSA), the workshop examined how telehealth could serve geographically isolated individuals and extend the reach of scarce health care providers and services. Workshop sessions covered a wide range of issues, including the operational difficulties of providing telehealth in rural communities, the challenge of securing payment, use by providers in different settings across the health care continuum, and the strengths and limitations of past evaluations. In the closing session, one attendee reminded participants that, ultimately, the technology is less important than those it serves (Nina M. Antoniotti, p. 128):

Telehealth is about the people, not the process. Public policy should not place barriers based on assumptions. For example, we are mired in discussions of presuming to know what patients want. Furthermore, we need to establish the methodology that HHS [the U.S. Department of Health and Human Services] would use to translate consumer momentum around mobile devices. Consumers push us to do things differently in health care, and we do it because it makes sense, has good outcomes, and engages patients.
Adoption Block

Telemedicine is an example of adoption block: Although the technology is feasible and highly promising, it cannot gain traction in the marketplace because its adoption threatens the interests of powerful institutions and groups, such as local health care practitioners and state licensing boards. Where parochial concerns do not exist and reimbursement is assured—for instance, in teleradiology—the technology has flourished. But in other settings, adoption of telemedicine has been severely constrained.

Telemedicine has the potential to increase provider efficiency, promote health care equity, and enhance access to care in geographically remote and underserved communities. But until sufficient will is mustered to break down political and regulatory barriers that are impeding its adoption, its promise will be largely unfulfilled.

References


