Fantastic Voyage: Questions from the 21st Century

As a child, did you like reading science fiction or watching Star Trek? If so, this issue is really a treat for you!

Robots the size of small VW bugs in the operating room assisting urologists in removing a prostate. Wireless endoscopy capsules, the size of large vitamin pills, touring through the small intestine, filming a scene straight out of Fantastic Voyage. Preimplantation genetic testing on one cell from an embryo. Molecular-targeted therapies for cancer.

This issue of The Permanente Journal will explore these and other exciting new technologies, devices, tests, and drugs, but it will only scratch the surface of the plethora of new technologies being developed in the 21st century. Many challenges for Kaiser Permanente (KP) arise from this exploding pace of development. Which new technologies should we deploy? Where and in how many medical centers? How do we retrain our physicians in these new procedures? Who are the appropriate patients to receive these new procedures? How do we monitor results?

The answers to these questions and the technology management process in KP will also be reviewed in this issue. This issue focuses on NEW technology, but we cannot lose sight of the fact that a recent study revealed that Americans in general receive medical procedures supported by evidence-based medicine only about half the time.1 The evidence-based technology management process has also been utilized in KP to address inadequate utilization of older technologies.

Finally, we also hope to help answer a burning question for clinicians—how do I keep up with such rapidly changing medical advancements? Resources to answer this question are in this issue.

Reference

Discoveries
The most important discoveries will provide answers to questions that we do not yet know how to ask and will concern objects we have not yet imagined.

—John N Bahcall, 1934-2005, American astrophysicist
Advances in Imaging—The Changing Environment for the Imaging Specialist

By John Rego, MD
KM Tan, MD

Over the last two to three decades, the demand for imaging services has blossomed at an unprecedented rate. New modalities have either been introduced as in magnetic resonance imaging (MRI) and positron emission tomography (PET) or significantly improved as in computed tomography (CT) and ultrasound (US).

The increasing sophistication of cross-sectional imaging with very rapid development and integration of interventional radiology into the clinical arena has had a dramatic impact on patient care. The imaging specialist now faces a remarkable transition in his/her work environment.

Bryan refers to two separate but related phenomena. The marked increase in information available from modality advances, and now available in three dimensions, accompanied by technology allowing extensive digital manipulation of such data presages a new era in medical imaging.

Digital data and technology have revolutionized the imaging field. The electronic acquisition, interpretation, transmission and storage of image data has not only increased access for patients but also benefits their referring physicians. Imaging interpretations are available earlier and more readily, and there is almost instantaneous access to these examinations on their office computers. This, of course, mandates an integrated information enterprise that all Kaiser Permanente (KP) Regions have now or will have soon. Picture archiving and communications systems (PACS), radiology information systems (RIS), and hospital information systems (HIS) all contribute to seamless acquisition of image data through PACS, which, together with information from the RIS and the HIS, result in rapid interpretation available to clinicians together with the original images pulled from archival storage. Thus, images and reports are at the right place at the right time.

This technology has inevitably resulted in increasing efficiencies, particularly during off hours, allowing one radiologist to offer interpretation coverage for 17 hospitals in Northern California. A similar situation prevails in Southern California (see page 47). It allows immediate access during the working day to subspecialty imaging expertise of multiple experts located throughout the Region and also allows the ability to provide interpretation services to some of the personnel-strapped Regions both within and outside of California.

Perhaps nowhere else in medicine has there been such rapid advance in technology than in CT scanning. With the advent of multidetector CT (MDCT) five years ago and, more recently volume CT (VCT), a relatively quiet revolution has taken place. CT scanners are now capable of obtaining 128 slices in less than one second. The entire chest, abdomen and pelvis can now be examined with submillimeter imaging in less than 15 seconds. This has led for the first time to true CT volume imaging where image reconstruction can take place in any plane with equal resolution.

We are just beginning to feel the impact of this very valuable tool in such areas as vascular imaging and virtual colonoscopy. The VCT has replaced peripheral

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diagnostic angiography in many centers and is poised to do the same for diagnostic coronary angiography. In the study of the colon, VCT has been shown to be superior to barium enema, approaching the sensitivity of colonoscopy in the detection of polyps larger than 9 mm.²

Advances in software have allowed almost instantaneous display of the images in shaded 3-D representations. This is proving invaluable in preoperative planning. The addition of CT fluoroscopy has allowed rapid, accurate real-time placement of biopsy needles, drainage catheters, and therapy devices.

As the technology advances, several vendors plan to introduce scanners that will acquire up to 512 images per half second with coverage of 12 cm. This will allow for perfusion imaging where viability of tissue can be evaluated. Coronary arterial and myocardial viability will be able to be evaluated simultaneously. Beyond 512 imaging, scanners are being tested that will use large-area detectors that will allow examination of the entire abdomen in just one pass of the x-ray tube.

Advances in MRI are equally as remarkable. As the 1.5T technology matures, there is new technology in the form of 3T-fieldstrength magnets that allow for faster, more detailed, and thinner imaging sections than its 1.5T counterpart. MRI is showing that it can compete with CT in noninvasive imaging of the heart. Multiplanar real-time images of the beating heart can now be obtained that allow for full, functional assessment of the heart. With contrast, perfusion studies can also be obtained.

MRI remains the imaging examination of choice for musculoskeletal and neurologic applications and will continue to compete with CT in evaluation of the vascular tree. And many new applications of MRI will spur further growth. For example, in the breast, with the use of gadolinium contrast agents, MRI is proving to be very sensitive for detection of small breast cancers. Its role in this regard is still being evaluated. When coupled with focused high-energy ultrasound, MRI can be used to guide noninvasive tumor therapies. It has shown its usefulness in treating such tumors and uterine fibroids and in limited applications of other visceral tumors.

Spurred on by miniaturization and by advances in computing power, the applications of ultrasound continue to grow. It is now possible to do high-quality ultrasound on devices the size of a laptop computer. Some devices in development are no larger than a PDA; these may indeed be the stethoscopes of the future. Three- and 4-D ultrasound have been further refined and are now being used in fetal imaging and ultrasound contrast imaging. Voice recognition and real-time image optimization (tuning of the image to the patient’s own acoustic properties) have improved patient workflow. With the pending approval of ultrasound contrast agents, ultrasound will compete with CT and MRI in the evaluation of the liver.

Interventional radiology continues to grow as procedures migrate from the OR to the IR suite. Stents and stent grafts have dramatically changed the practice of vascular surgery. Vascular surgeons and interventional radiologists have joined forces in many labs with a merging of their two specialties. Percutaneous tumor ablation, stabilization of vertebral body fractures, tumor embolization, venous ablation and recanalization are all procedures now common to the interventional labs.

New flat panel detectors have improved image quality and decreased radiation dose. New rotation angiographic techniques have allowed 3-D vascular image displays. With tube rotation it is now possible through post processing to obtain multislice CT images from the IR equipment.

Digital image acquisition has replaced film throughout the Radiology Department. Digital detectors are now used instead of film to allow immediate image review. This advance has lead to an increase in image quality and a 50% decrease in imaging time. Dual-energy subtraction has allowed improved evaluation of the lungs by subtraction of the bony structures. Additional application of computer-aided diagnosis (CAD) has led to a 10% increase in tumor detection in 64 slice CT scanner now used for cardiac work.
the chest and breast. This same application is being trialed in CT colonoscopy as well.

Thus several trends are becoming clearer. The earlier and more frequent use of imaging will continue with a shortening of the initial clinical evaluation. As indicated above, the 64-slice CT scanner will allow immediate evaluation of a patient’s chest pain, allowing differentiation between a benign situation and the possibility of a heart attack, an aneurysm, or a pulmonary embolism.

Technology will continue to drive care from the hospital. Decreasing cost and size of equipment will allow CT and MRI to devolve outside the hospital Radiology Department into freestanding situations.

The readily available image distribution process ironically will decrease reliance on the radiologist and there will be an enhanced shift to proactive, prophylactic screening in imaging. Computer-assisted detection and diagnosis in the areas of breast, lung, and colon disease are but a harbinger of such use in all clinical areas. Last but not least, functional and metabolic imaging is becoming a reality, and the promise of genetic and molecular marker imaging is not far behind.

One issue merits ongoing discussion and research. Advances in technology serve as one of the most important drivers of health care spending growth. Currently in the United States, medical care consumes more than 14% of the gross domestic product and is likely to reach 17.7% by 2012.\(^3\)

Increases in the supply of specific technologies such as CT and MRI are associated with higher numbers of procedures per population and with consequent higher health care spending. Experience has shown that co-existence of CT and MRI is not complementary but supplementary. Thus, MRI availability does not offset CT use.\(^4\)

While there may be a legitimate argument for bypassing the current progression of imaging tests from the least expensive to more costly examinations in favor of expensive high-tech imaging as a first-time test that provides more information, the effect is a distinct overall increase in health care spending. With the number of uninsured Americans approaching 50 million and with more of us unable to afford soaring health care costs, it is appropriate to question to what extent we can and should continue to spend dollars in pursuit of increasing diagnostic capabilities that in turn increase the probability of detecting multiple benign abnormalities and the consequent need to resolve them. Can we afford an “arms race” among manufacturers as they continue to outdo one another in the increasing detail and sophistication of their imaging devices? Is it appropriate to tolerate surging health care costs, especially in view of the lack of well-planned cost effectiveness and outcomes studies to support the increasing use of such modalities? \(\text{❖}

References


Inventions

Our inventions mirror our secret wishes.

—Mountolive, Lawrence Durrell, 1912-1990, Anglo-Irish novelist and playwright
Genetic Services in the KP Southern California Region: Delivering the Promises of Tomorrow Today

Abstract
The impact of advances in molecular biology over the past 25 years—especially the completion of the Human Genome Project—touches every branch of medicine and will continue to have profound influence on medical practice. Advances in genetic technology are changing the traditional patient/doctor paradigm. For some medical conditions, current genetic technology and predictive testing enable us to offer medical management before a patient is diagnosed with a disorder. However, advances in genetic technology impose on all clinicians the added requirement of identifying patients who may benefit from having access to this technology. Kaiser Permanente (KP) provides a unique, integrated approach to this challenge by serving as a model for delivery of genetic services. This article outlines the history and current status of genetic services provided in the KP Southern California Region and summarizes current and future developments in medical genetics technology.

Dawn of a New Era
The integral role of genetics in everyday medical practice is the result of more than five decades of revolutionary clinical and molecular research. The impact of advances in molecular biology over the past 25 years—especially the completion of the Human Genome Project—touch every branch of medicine and will continue to profoundly influence medical practice. Application of genomics to the study of responses to pharmaceuticals is opening new opportunities in drug development and in pharmacogenetic tools for lowering risks of drug therapy and for increasing its benefits. While genetic technology continues to evolve, however, clinicians face the daunting task of integrating emerging technologies into daily medical practice to improve the health and welfare of patients. As medical genetics gained unparalleled prominence in the 1990s, Kaiser Permanente (KP) has enhanced its unique system of integrated health care services by becoming a national leader in delivering cutting-edge genetic services to KP members. This article outlines the history and current status of genetic services available in the KP Southern California Region (KPSC) and summarizes current and future developments in medical genetics technology.

From Humble Beginnings to State-of-the-Art Practice
Clinical geneticist Nancy Shinno, MD—who is now KPSC Chief of Regional Genetic Services—started her KP career in 1978 as one of only four KPSC clinical geneticists. In those early years, KP geneticists divided their time between medical genetics practice and pediatrics. Moreover, the practice of genetics primarily consisted of evaluating children with dysmorphic features and developmental delay and counseling women about the risks of advanced maternal age. Other than cytogenetic analysis performed to determine chromosome abnormality, few options existed for prenatal diagnosis of genetic disorders.

Now Dr Shinno leads the KPSC Regional Genetics Department, which includes 8 full-time medical geneticists, 22 genetic counselors, a regional genetic screening program, and a regional metabolic genetics program. The KPSC Genetics Department provides genetic ser-
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vices to KP members at every KPSC medical center. The “menu” of available genetic tests has expanded exponentially, and the practice of genetics has grown beyond the realm of prenatal and pediatric genetics to include cancer genetics and neurogenetics, among other areas (see Tables 1 and 2). KPSC geneticists and genetic counselors also participate in programs where genetic disorders are managed by other specialists, such as those practicing in the craniofacial service, the sickle-cell disease center, and clinics that evaluate patients for neuromuscular or neurodegenerative disorders.

The impact of genetic technology on diagnosis and management of genetic disorders over time is clearly illustrated by treatment of Fabry disease, an X-linked recessive storage disorder first described in 1898. The disorder causes painful, disabling crises in boys as young as ten years of age; progressive damage to the kidneys, heart, and central nervous system, among other organs; and generally results in renal failure that can lead to early death in men in their thirties and forties. Fabry disease is caused by mutation in the alpha galactosidase A (GAL) gene.

This genetic mutation causes deficient activity of the alpha galactosidase enzyme. This deficiency results in progressive accumulation of glycosphingolipids, especially in vascular endothelium, leading to ischemia and infarction of small vessels and resultant renal, cardiac, and cerebrovascular dysfunctions.

In 1978, when Dr Shinno counseled a young woman whose brother and a maternal uncle had Fabry disease, doctors could offer such women little other than the information that they had a 50% chance of being a carrier of the condition. At that time, Fabry disease could be diagnosed in the woman’s brother by using enzyme analysis of leukocytes to identify alpha galactosidase deficiency, but this diagnostic test could not reliably diagnose the carrier state. Prenatal diagnosis using enzyme analysis could be used to detect an affected male fetus, but no treatment (other than kidney transplantation) was available for any affected sons the woman might bear.

By the early 1990s, scientists had mapped the gene for Fabry disease, and DNA analysis was available to inform women whether or not they were carriers of the disease. If results of DNA analysis were negative, the woman had no need to worry about bearing sons destined to have the disorder; if results of the test were positive, the woman could have prenatal diagnosis using sequence analysis, which could detect nearly 100% of mutations in the GAL gene.

By 2003, medical geneticists could inform a carrier patient that enzyme replacement therapy (a drug spinoff from identifying the gene) was available for her affected sons to help prevent renal failure, cardiac and cerebrovascular sequelae, and pain.

A KP multidisciplinary Fabry Disease Advisory Panel including experts from the genetics, cardiology, neurology, nephrology, ophthalmology, and gastroenterology departments meets regularly to discuss and create management guidelines and to review nonclassic cases of Fabry disease. Treatment of this disease illustrates the potential for treatments derived from expanded knowledge about the genetic basis for disease and developed through new technology for pharmaceutical development. Indeed, the story of Fabry disease illustrates how advances in genetic technology have transformed management of this condition from simply offering in-

Table 1. Scope of KPSC Regional Genetic services

<table>
<thead>
<tr>
<th>Services</th>
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<tbody>
<tr>
<td>Prenatal/Reproductive Genetics testing</td>
</tr>
<tr>
<td>Genetic Screening</td>
</tr>
<tr>
<td>Neonatal/Pediatric Genetics</td>
</tr>
<tr>
<td>Adult Genetics (including Cancer and Neurogenetics)</td>
</tr>
<tr>
<td>Metabolic Genetics</td>
</tr>
<tr>
<td>Craniofacial Service</td>
</tr>
<tr>
<td>Genetic Testing Laboratory</td>
</tr>
</tbody>
</table>

Table 2. KPSC Regional Genetics mission statement

The primary aim of the KPSC Regional Genetics Program is to help individuals and families faced with genetic disorders to live and reproduce as normally as possible. Our goal is to ensure that high-quality services are available and accessible to all patients who require care. We strive to reduce morbidity and mortality, to alleviate the suffering associated with genetic and congenital disorders, to improve health and pregnancy outcomes, and to optimize life options for people affected by a genetic disorder.
Genetic Services in the KP Southern California Region: Delivering the Promises of Tomorrow Today

The use of enzyme replacement to treat certain genetic conditions has increased by nearly 2000%, and the number of fluorescent in situ hybridization (FISH) procedures has increased by more than 500%, while the number of inhouse molecular tests sent to outside laboratories has decreased in the number of prenatal specimens has remained fairly consistent. Moreover, during the past five years, the Regional Genetic Testing Laboratory has seen a dramatic decrease in the number of molecular tests sent to outside laboratories while the number of inhouse DNA tests has increased even more dramatically (Figures 1 and 2).

Genetic tests are often more complex than other types of medical tests. Testing for genetic susceptibility to disease (eg, examination of breast cancer susceptibility genes BRCA1 and BRCA2) is inherently complex because of its probabilistic and familial nature. Tests of this type identify empirical risks on the basis of genetic linkage studies of populations, not studies of risk in individual persons. This type of population testing has social and ethical consequences that extend beyond medical management and reveals information that affects not only the patient but also the patient's blood relatives. For this reason, genetic counseling is always an integral part of genetic testing. At KPSC, an outstanding team of 22 genetic counselors work alongside SCPMG medical geneticists to provide pedigree collection and risk assessment; education about genetic diseases and genetic testing options; discussion of options for disease manage-

Table 3. Types of genetic tests

| Diagnostic Tests: Used to confirm or exclude suspected genetic conditions (eg, Duchenne muscular dystrophy) in symptomatic persons of any age. |
| Predictive Tests: Offered to asymptomatic persons concerned about possible susceptibility to a genetic disorder. Two types:  |
| - Presymptomatic, where eventual development of symptoms is certain, eg, Huntington disease. |
| - Predispositional, where eventual development of symptoms is likely but not certain, eg, inherited susceptibility to breast and ovarian cancer. |
| Carrier Tests: Used to identify healthy persons who have a genetic mutation coding for an autosomal or X-linked recessive disorder which puts their children at risk for having the disorder. Carrier tests may be conducted in persons with a family history of the condition or in ethnic groups known to have a higher carrier rate for the condition (eg, cystic fibrosis). |
| Prenatal Tests: Used to diagnose genetic conditions in the fetus. Offered to pregnant women who, because of any conditions (maternal age, personal or family history, ethnicity, suggestive results of either multiple-marker screening or fetal ultrasound), are at increased risk for having a child with a genetic condition or congenital defect. |
| Newborn Screening Tests: Used in newborns to determine whether they are at increased risk for specific genetic conditions that usually need immediate treatment. |
| Pharmacogenetic Tests: Used to determine how a person’s genetic makeup may affect that person’s reactions to specific drugs. These tests may help clinicians to prescribe drugs that are most effective and cause the least side effects. |
| Preimplantation Genetic Diagnosis (PGD): Used to test embryos for genetic disorders before transfer of the embryo to the uterus. PGD has limited application and is considered on a case-by-case basis. |

Table 4. Most common cancer susceptibility syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Cancer Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBOC</td>
<td>BRCA1, BRCA2</td>
<td>breast, ovarian, prostate, others</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>p53</td>
<td>breast, brain, adrenocortical, sarcoma, leukemia, others</td>
</tr>
<tr>
<td>FAP</td>
<td>APC</td>
<td>colorectal, duodenal, thyroid, others</td>
</tr>
<tr>
<td>HNPCC</td>
<td>MLH1, MSH2, MSH6</td>
<td>colorectal, endometrial, stomach, ovary, others</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
<td>hamartoma of skin, breast, thyroid, oral mucosa, and intestine</td>
</tr>
</tbody>
</table>
health systems

Special Feature

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Figure 1. Graph shows number of samples sent by KPSC Regional Genetics Testing Laboratory for DNA testing outside KP during years 1991 through 2005. Graph produced by Michael Bucher, and used with permission.

Figure 2. Number of inhouse DNA tests done at KPSC Regional Genetics Testing Laboratory during years 2000 through 2005. Graph produced by Michael Bucher, and used with permission.

Cancer Genetics

For decades, physicians have been able to identify families that have clearly hereditary patterns of cancer; however, physicians had little to offer these families other than recommending vigilance toward all family members without knowing who was (or was not) at risk. That situation changed in the past decade, thanks to the discovery and mapping of several genes associated with susceptibility to cancer. Commercial testing for familial adenomatous polyposis (FAP, the most thoroughly characterized hereditary form of colorectal cancer) was first made available in 1995 and was closely followed by testing for BRCA1 and BRCA2 (breast cancer susceptibility genes 1 and 2)—testing which first became available in 1996—and testing for hereditary nonpolyposis colorectal cancer (HNPCC). Opportunities for commercial and research testing for other cancer syndromes continue to evolve (see Table 4). KP has always

...ment, treatment, and surveillance; psychosocial support; and case management.

The KPSC Genetic Screening Program administers the California Expanded AFP Screening Program as well as the Regional Cystic Fibrosis (CF) Program and the Newborn Screening Program. In California, all pregnant women are offered prenatal “multiple marker screening” through the California Expanded AFP Program. The current panel reports a detection rate of 70% for Down syndrome and detection rates ranging from 85% to 97% for neural tube defects (depending on the type of neural tube defect). “Quad” screening, which adds another analyte to the assay, is under development and is expected to substantially improve prenatal detection rates for Down syndrome over the current “triple screen.” Prenatal CF carrier screening is offered to women on the basis of their ethnicity or on request. KP members who receive positive test results are immediately referred for genetic counseling to help them understand their risks, evaluate their options for additional testing, and make informed medical and personal decisions about having additional genetic tests.

KPSC also participates in the California Newborn Screening Program, which has for many years been screening newborns for phenylketonuria (PKU), sickle-cell anemia, congenital hypothyroidism, and galactosemia. Since its inception, the program has screened virtually all babies born to KPSC members. The program was expanded in 2005 to screen for more than 40 additional disorders through use of tandem mass spectrometry. Among the disorders detected by this method are medium-chain-acyl CoA dehydrogenase (MCAD) deficiency and glutaric acidemia type I (GA1).
been a leader in the area of cancer genetics and was one of the first healthcare organizations in the nation to address the issues related to BRCA1/BRCA2 testing. In 1997, the National KP Guidelines for BRCA Counseling and Testing were among the first such guidelines developed in the United States. Geneticists and genetic counselors from KPSC were key contributors to development of that guideline, and today these professionals continue to provide comprehensive risk assessment, genetic testing and interpretation, and management information to patients who are at risk for hereditary cancer susceptibility, as well as to their families.

Diagnosis and management of FAP are excellent examples of how genetic technology has substantially changed the way that hereditary cancer susceptibility is diagnosed and treated today. FAP is an autosomal dominant condition which affects approximately 1 in 5000 persons and is characterized by development of numerous (often more than 1000) colon adenomas; virtually all affected patients are at risk for having colorectal cancer by age 40 years. Before 1995, diagnosis of FAP was based on family history of either polyposis, early colon cancer, or both, and sometimes based on presence of extracolonic characteristics (eg, congenital hyperpigmentation of retinal epithelium). Because of the early manifestations of the disorder, all children of affected parents were scheduled for annual endoscopic examination beginning around ten years of age. Before 1995, diagnosis of FAP was based on family history of either polyposis, early colon cancer, or both, and sometimes based on presence of extracolonic characteristics (eg, congenital hyperpigmentation of retinal epithelium). Because of the early manifestations of the disorder, all children of affected parents were scheduled for annual endoscopic examination beginning around ten years of age.

Because each child had a 50% chance of being affected, half of the children receiving endoscopy had the procedure unnecessarily. After genetic testing became available and the family mutation could be identified, children at risk could be tested; and only those carrying the family mutation would need to be screened for colon cancer. This genetic testing technology thus spares unaffected children from being tested and allows families and the healthcare systems to focus their resources where they are most needed.

Thanks to recent developments in molecular diagnostics, the rate of detecting the mutations in FAP families has increased from about 80% (in the 1990s) to 90% today.

### The Vision of Pharmacogenetics and Pharmacogenomics: The Right Drug for the Right Patient

Pharmacogenetics is the study of variations in DNA sequence related to drug action and disposition and includes study of the enzymes involved in drug metabolism as well as the transporters involved in the absorption, distribution, and excretion of drugs. Pharmacogenomics is the study of all genes that affect the body’s response to drugs; pharmacogenomics is thus the intersection of pharmacology and genomics. Although the terms pharmacogenomics and pharmacogenetics are often used interchangeably, pharmacogenomics is a broader term because it applies to all genes.

### Pharmacotherapy for Heritable Disorders

Recombinant versions of enzymes have been developed for treating several heritable disorders of lysosomal storage. Enzyme replacement therapy is available for patients with Gaucher disease, Fabry disease, and some forms of mucopolysaccharidosis (MPS). Other forms of enzyme replacement therapy may soon be approved for treating Pompe disease and another type of MPS (see Table 5).

Throughout California, semianual collaborative videoconferences have been held by KP geneticists and other specialists (eg, cardiologists, neurologists, nephrologists, ophthalmologists, and gastroenterologists) who treat these patients.

### Table 5. Enzyme Replacement Therapy commercially available or pending FDA review

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Disorder</th>
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<tbody>
<tr>
<td>imiglucerase (Cerezyme)*</td>
<td>Type 1 Gaucher disease</td>
</tr>
<tr>
<td>laronidase (Aldurazyme)*</td>
<td>Mucopolysaccharidosis I (MPS I)</td>
</tr>
<tr>
<td>agalsidase beta (Fabrazyme)*</td>
<td>Fabry disease</td>
</tr>
<tr>
<td>galafusfase (Naglazyme)*</td>
<td>MPS VI (Maroteaux-Lamy syndrome)</td>
</tr>
<tr>
<td>alpha-glucosidase</td>
<td>Pompe disease</td>
</tr>
<tr>
<td>iduronate-2-sulfatase</td>
<td>MPS II (Hunter syndrome)</td>
</tr>
</tbody>
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*Commercially available in the United States as of late 2005.

### Table 6. Minimum requirements for obtaining family medical history

<table>
<thead>
<tr>
<th>Requirement</th>
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<tbody>
<tr>
<td>Obtain family history information on at least three generations.</td>
</tr>
<tr>
<td>Ask about all individuals in both sides of the patient’s family and record pregnancy history, including losses/stillbirths/neonatal deaths, age at diagnosis of significant disease, current age (or age at—and cause of—death).</td>
</tr>
<tr>
<td>Ask about history of mental retardation or developmental delay, birth defects, known genetic disorders.</td>
</tr>
<tr>
<td>Record ethnicity and race.</td>
</tr>
<tr>
<td>Record consanguinity.</td>
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Videoconference participants review the newer enzyme replacement products as well as issues surrounding therapy. This interactive approach provides an optimum perspective on complex diseases, enables sharing of information, and helps clinicians who are making treatment decisions regarding enzyme replacement therapy.

**The Promise of Personalized Medicine**

News articles have heralded the approach of personalized medicine, a vision of the future wherein type and dose of medication will be chosen on the basis of each patient’s own genetic profile as determined by pharmacogenetic pretesting. This envisioned future will probably occur in small steps, because testing is not yet widely available for most genetic variants and because outcome data must first be collected to guide prescription adjustments based on pretesting. This futuristic model of personalized medicine must also account for multiple factors that can affect gene expression.

Pharmacogenetic information has already been added to the FDA-approved labeling of some medications. Many others will follow, adding new facets to treatment decisions in individual cases. In addition, pharmacogenomic analysis conducted during the drug development process will result in more accurately targeted drugs with more limited toxicity. This achievement may bring new therapies to the consumer market, because improved efficacy and lessened toxicity could justify FDA approval of drugs which could not have been approved for less-well-defined target populations.

During the past five decades, research has led to considerable increase in knowledge concerning the metabolizing enzymes affected by polymorphisms of single genes. Examples of these enzymes include:
- N-acetyltransferase (NAT2), related to alterations in pharmacokinetics of isoniazid, hydralazine, procainamide, and sulfonamides
- cytochrome-P450 isoenzymes, such as CYP2D6, CYP2C19, and CYP2C9, which affect metabolism of many drugs
- UDP-glucuronosyl transferases (UDP-GT), which has an isoenzyme (UGT1A1) that converts the active metabolite of irinotecan to an inactive glucuronide.

Patients with one of these polymorphisms may be at increased risk for adverse reactions or for inefficacy of the substrate drugs when these drugs are used at usual doses.

With new pharmacogenetic applications and expanded information about associations between drug therapy and genetic variations, the challenge presented to KP includes the need for careful, evidence-based evaluation regarding use of pharmacogenetic testing in drug therapy. This evaluation will require the coordinated efforts of physicians, clinical laboratory staff, and pharmacy staff. In most instances, we will find value in development of evidence-based guidelines, educational tools, and internal KP review by the Biotechnology and Emerging Pharmaceutical Technology Assessment Committee (BEPTAC), physician committees, and the Pharmacy and Therapeutics Committee.

**Genetic Testing and Drug Therapy**

At least two types of genetic testing will be used in pharmacogenetic applications that affect choice of drug therapy.

One such type of testing measures genetic variation in a disease, such as mutations in tumor tissue. One of the best-known examples of gene testing related to drug therapy is testing of tumor tissue in metastatic breast cancer patients as a determinant of whether trastuzumab (Herceptin, Genentech, South San Francisco, CA) might be effective. Overexpression of the HER2 protein has been found in some human primary tumors and has been identified in 25% to 30% of patients with breast cancer. Available methods of testing include an immunohistochemical (IHC) assay to test for overexpression of HER2 protein and a FISH test using a DNA probe to determine HER2 gene amplification. Testing has become both a standard feature of treatment plans and requisite for use of trastuzumab in a specified subset of patients diagnosed with metastatic breast cancer.

The other type of genetic testing is testing for genetic variations in an individual person. An example of such variation is the gene variant for UGT1A1 enzyme, which converts the active metabolite of irinotecan (Camptosar; Pharmacia, Peapak, NJ), indicated for metastatic colorectal carcinoma) to an inactive metabolite. This polymorphism (UGT1A1*28) leads to decrease in UGT1A1 enzyme activity, which in turn leads to increased irinotecan toxicity (eg, severe neutropenia). About 10% of North Americans are homozygous for the polymorphism and are at increased risk for this toxicity. Another 40% of the North American population are heterozygotes and may also have some increased risk for toxicity. The FDA has recently added this information to the irinotecan product label.* Oncologists, pharmacists, laboratory personnel, and geneticists are interacting to determine how to use this pharmacogenetic information most effectively.
The Family Medical History: A Timeless Tool

Although genetic technology continues to evolve at an unprecedented pace, the family medical history remains a valuable clinical tool in delivery of genetic services to our patients. Indeed, one forecast has stated that “Personal and family [medical] history will continue to be the key indicator for clinical use of genetic tests.”

Collection and interpretation of information on family medical history is essential for several purposes: to identify persons at risk for genetic conditions, to determine genetic testing options, to interpret results of genetic tests, and to choose appropriate options for clinical case management. The FAP example presented above is a perfect illustration of how knowing a patient’s family medical history affects diagnosis and management of a genetic condition.

Physicians in all specialties will face increasing demands “to explore family [medical] history, explain genetic testing options, and separate genetic hype from reality for their patients—roles for which physicians currently receive little or no training.”

Recently, several professional organizations have focused on increasing genetic competency among primary care practitioners. The National Coalition for Health Professional Education in Genetics (NCHPEG) has defined core competencies in genetics for all health professionals and has developed education tools to promote integration of genetics into healthcare practice. The American Academy of Family Physicians chose genomics as their Annual Clinical Focus (ACF) for 2005 and invited Francis Collins, MD, Director of the Human Genome Project, to kick off the program; and the CDC declared Thanksgiving 2004 as “Family History Day” to launch its Family History Initiative.

The family medical history should include information on at least three generations from both sides of the family (see Table 6). Physicians must recognize that family history is dynamic. As relatives age, they may be diagnosed with new disorders that were not part of the original history collected for the patient. For data on family medical history to be accurate, it must be updated regularly. Collecting and updating information on family medical history should not be the sole responsibility of primary care practitioners, however. Because some KP members rarely see a primary care practitioner, all clinicians should seize the opportunity to collect and update information about their patients’ family medical history.

KP HealthConnect will provide an opportunity for collecting and tracking some data on family medical history. Moreover, a KP interregional committee of genetics specialists is currently exploring options for developing expanded databases of family medical history and pedigree.

We hope that these initiatives will allow family history interpretation software to become widely available to assist primary care practitioners in identifying patients at risk for genetic conditions and to improve clinical care of these patients. Until those tools are universally available, clinicians should familiarize themselves with some of the more common “clues” that suggest the need for a referral to the genetics service (Table 7).

Present and Future Evaluation of Genetic Technology at KPSC

The KPSC Regional Genetics Department works closely with many other departments and processes to ensure that the following occur:

- Decisions regarding introduction of new genetics technology are evidence-based
- All aspects of service quality and cost are considered during the planning and implementation process
- An ongoing management structure for existing technologies is provided. Groups who interact with the KPSC Regional

<table>
<thead>
<tr>
<th>Table 7. Genetic “red flags” in the family medical history</th>
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<tr>
<td>Children with birth defects, developmental delay, unexplained short stature, clinically significant hearing loss, unusual dermatologic conditions, ambiguous genitalia, or tumors with possible hereditary component (eg, retinoblastoma, Wilms’ tumor)</td>
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<tr>
<td>Family history of mental retardation, birth defects, or known genetic disorders (eg, muscular dystrophy, hemophilia, neurofibromatosis)</td>
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<td>Family history of multiple pregnancy losses, stillbirths, or unexplained neonatal death</td>
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<tr>
<td>Consanguinity</td>
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<tr>
<td>Evidence of autosomal dominant (vertical) transmission</td>
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<td>Evidence of autosomal recessive (horizontal) transmission</td>
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<tr>
<td>Three or more relatives (on same side of family) with same disorder (eg, colon cancer)</td>
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<tr>
<td>Early age at diagnosis of common cancer (eg, breast or colon cancer at age &lt;50 years)</td>
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<tr>
<td>Multiple primary cancers in same individual</td>
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<tr>
<td>Constellation of tumors consistent with specific cancer syndrome (eg, breast and ovary, or colon and endometrium, in the same side of the family)</td>
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KP HealthConnect will provide an opportunity for collecting and tracking some data on family medical history.
Genetics Department include National KP and KPSC Medical Technology Assessment and Deployment Committees, the Biotechnology and Emerging Pharmaceutical Technology Assessment Committee, the Regional Laboratory, and the Research and Evaluation Department.

Advances in genetic technology are changing the traditional patient-doctor paradigm. Because of current genetic technology and predictive testing, medical management is now available for some conditions before they are diagnosed in a patient, and diagnosis is possible for many conditions for which no effective treatment currently exists. In both situations, genetic counseling of patients is imperative for helping them and their families to understand this complex information. In the future, evolving genetic technology will allow physicians to manage their cases on the basis of each patient’s individual genetic makeup, the disorders to which these patients are predisposed, and how these patients respond to treatment.

The impressive power of genetic technology brings with it an equally impressive three-part responsibility: equitable access, clinically responsible care, and timely use of genetic technology for patients who may benefit from it. Collecting, documenting, and acting on information about each patient’s family medical history are key factors in this equation. The physicians and counselors at the KPSC Regional Genetics Department are already delivering on the promises of genetic technology and will continue to combine powerful, state-of-the-art medicine with a personal touch and with the same excellence that exemplifies genetic services in each KP region.

References

Glossary
- Genetics is the study of single genes and their effects.
- Genetic Medicine includes the diagnosis and treatment of conditions caused by mutations in a single gene (eg, Huntington disease) or chromosomal abnormality (eg, Down syndrome). Genetic counseling, genetic testing, and genetic-disease management are services that have been associated with genetic medicine practice.
- Clinical geneticists are Board-certified or Board-eligible physicians who have completed a fellowship approved by the American Board of Medical Genetics. The American Board of Medical Genetics, recognized by the American Board of Medical Specialties in 1991, certifies physicians in clinical genetics along with physicians and PhDs in clinical biochemical genetics, clinical cytogenetics, and clinical molecular genetics. In the past, clinical geneticists were interested primarily in dysmorphology and evaluation of children with birth defects, mental retardation, or both. Although this interest continues to be a part of their practice, clinical geneticists now engage in a wide range of clinical endeavors involving patients of all ages.
- Genetic Counselors are medical professionals trained in all areas of medical genetics who have completed a master’s degree program accredited by the American Board of Genetic Counseling and who are Board-certified or Board-eligible. In addition to collecting and interpreting information of a patient’s family history, genetic counselors educate and counsel patients about genetic disorders, inheritance patterns, genetic testing options, interpretation of test results, and the medical and social implications of genetic disorders. Genetic counselors work under the supervision of, and in collaboration with, clinical geneticists. Genetic counselors provide preconception and prenatal genetic counseling to determine family history of birth defects or inherited conditions, possible teratogenic exposure, consanguinity, suspected personal or family history of cancer susceptibility, and other conditions.
- Genomics is the study of the whole genome—how individual genes interact with each other and how they may interact with the environment to spur development of disease. When genomics is fully developed as a field, genetics will be a subset of genomics, and genetic medicine will be part of the prevention, diagnosis, and treatment of all disease, not just genetic disorders.
Wonder

Wonder was the motive that led people to philosophy. Philosophy is to the cure of the soul what medicine is to the cure of the body. Wonder is a kind of desire in knowing. It is the cause of delight because it carries with it the hope of discovery.

—Thomas Aquinas, circa 1225-1274, Italian Catholic philosopher and theologian
Kaiser Permanente Southern California Regional Technology Management Process: Evidence-Based Medicine Operationalized

By Joanne Schottinger, MD
Richard M Odell


Introduction
Kaiser Permanente (KP) has a robust process for evaluating, deploying, and monitoring new types of medical technology, including devices, equipment, diagnostics, and procedures. This process provides guidance and management of new and existing medical technology to ensure that physicians of the Southern California Permanente Medical Group (SCPMG) can provide state-of-the-art care. The success of the process depends on participation of a variety of internal professional and physician experts as well as other internal groups, such as the Interregional New Technologies Committee, Laboratory Committees, and Pharmacy Committees.

The process of managing medical technology uses three teams of physicians and support staff: the Medical Technology Assessment Team (MTAT), the Medical Technology Deployment Strategy Team (MTDST), and the Regional Product Council (RPC). The medical technology management process seeks to evaluate medical technology in a timely manner, using principles of evidence-based medicine and focusing on efficacy, safety, and expected improvement in health outcomes. The evaluation process also provides analytical and tactical support to SCPMG physicians by assisting them with systematic, well-thought-out deployment of medical technology. The final component of the process considers benchmark standards to coordinate purchase of the technology while ensuring that KP leverages its collective purchasing power, and provides appropriate vendor support.

Over the past two decades, the process of managing new technology in the KP Southern California Region has evolved continuously. Initially, in 1983, a Medical Technology Committee was formed to evaluate requests of local medical centers for regional approval to purchase capital medical equipment. At that time, much focus was directed on new types of imaging technology, such as computed tomography (CT) or magnetic resonance imaging (MRI).

In 1995, the Technology Assessment and Guidelines (TAG) Unit was developed to support the committee by providing evidence-based evaluation of new technology. In 1998, the California legislature enacted the Friedman-Knowles Act, which set the stage for independent medical review of coverage decisions for individual health plan enrollees. The Medical Technology Inquiry Line was created in the KP Southern California Region as a one-stop location for giving clinicians prompt access to objective, evidence-based medical information on new technology. With the support of the Permanente Federation, this service was expanded to include support for KP regions outside California.

In 2000, a process called the Medical Technology Management Process was implemented to connect the discipline of evidence-based evaluation of medical technology with a strategy for planned equipment purchase and deployment. Figure 1 shows the groups currently participating in this process, the components of which include assessing and deploying medical technology as well as responding to inquiries about it.

Technology Assessment

The Medical Technology Assessment Team (MTAT) performs critical analysis of published, peer-reviewed medical literature to evaluate the evidence supporting use (or avoidance) of specific types of technology for medical diagnosis or treatment. Assessment of new tech-
nology includes describing the specific health problem, the population of concern, the new technology, any alternative interventions, and the desired health outcomes. The medical problem of interest is described precisely and systematically with input from clinicians practicing in specialties relevant to the specified condition.

One of the analytical staff uses PubMed (an online bibliographic resource) to search the medical literature. The published medical literature is searched also to identify any previous assessments that may have been conducted by other organizations that use evidence-based methodology (for example, the Emergency Care Research Institute, Blue Cross/Blue Shield, or Hayes, Inc, an independent assessor of health technology). Information is sought also from government agencies, such as the US Food and Drug Administration (FDA), National Institutes of Health (NIH), National Cancer Institute (NCI), Centers for Disease Control and Prevention (CDC), and from medical specialty societies.

The MTAT carefully evaluates the quality of available evidence by thoughtfully considering such factors as number of studies and subjects, quality of investigation (Figure 2), consistency of study results, certainty and magnitude of possible benefits and harms, and number of potential candidates for a specified intervention. Stating the rationale for its conclusion, the MTAT develops and forwards to interested specialty groups a recommendation based on the sufficiency of the evidence.

**Technology Deployment**

Technology whose use is supported by available evidence is also recommended by MTAT to the Medical Technology Deployment Strategy Team (MTDST), which considers the logistics of deployment, including forecasting the need and uses for the technology, developing a business case for its use, determining requirements for training and credentialing staff who will use the technology, and defining processes for monitoring the quality of the technology’s outcomes. The Regional Product Council (RPC) is responsible for acquiring, standardizing, and budgeting for medical equipment. The RPC communicates with KP’s geographic service areas in Southern California.

This process of evaluating, recommending, planning, acquiring, and monitoring use of new medical technology is tied together and is administratively coordinated by the Joint Chairs Committee (a group which includes the Chair and Cochairs of the MTAT, MTDST, and RPC). The Joint Chairs Committee ultimately makes regionwide recommendations about new technology.

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**Figure 1.** Diagram illustrates the KP Southern California Region technology management process.
after carefully consulting with KP internal experts, chiefs groups, regional clinical committees, and clinical technology committees. At their meetings, the medical directors and medical group administrators receive regular updates on new technology, including capital requirements as well as implications for future space planning.

**Responding to Inquiries about Technology**

Physicians or Member Services Representatives with a specific patient case question or leaders with questions about new technologies can easily access informational resources on new technology by contacting the KP Southern California Region Technology Inquiry Line at 626-405-5138 or by sending an electronic inquiry to Med-Technology-AGU, Scal (KP e-mail) or scal.med-technology-agu@kp.org (Internet access). Questions can range widely—from the newest technology for targeted cancer therapy or drugs still in clinical trials to the oldest technologies—and ask, for example, “What is the role of leeches in medical therapy?” and “How can we acquire leeches appropriate for medical use?”

In response to the inquiry, the technology assessment group sends an electronic file containing several components:
- a summary and analysis of published information
- a reference list with published abstracts obtained from MEDLINE
- assessments obtained from other evidence-based organizations, if available; and
- information on FDA/Medicare coverage.

The inquiry line receives about 700 inquiries per year, about a third of which originate from outside California. Maintaining assessments and responses in a database enables most inquiries to be answered within 24 hours.

**The KP Interregional New Technologies Committee**

Technology that may have programwide application is also assessed by an interregional KP group, the Interregional New Technologies Committee. This group, chaired by the Permanente Federation Associate Executive Director for Quality and Program Improvement, includes physician-representatives from each KP region, Program Offices, the Care Management Institute (CMI), and from Kaiser Foundation Hospitals benefits and regulatory services, legal counsel, public affairs departments, and ethics advisors. The INTC tracks emerging technology as it is developed for entry into the marketplace.

On the basis of the published literature reviewed, the INTC can issue any of three types of recommendation:
- Sufficient evidence shows that use of the technology is medically appropriate for select patients
- Insufficient evidence exists for the committee to determine whether use of the technology is medically appropriate for any patient; or
- Sufficient evidence shows that use of the technology is generally not medically appropriate for any patient.

Recommendations and discussion of the rationale for new technology discussed by the INTC are available on the clinical library Intranet site, [http://cl.kp.org/](http://cl.kp.org/). These materials are filed under Clinical Practice Guidelines as the last item (New Clinical Technologies) and can be searched either chronologically or alphabetically. Table 1 lists some recent examples of technology reviewed by the INTC along with its recommendations.

**Evaluation of New Drugs**

Assisted by monographs prepared by KP National Drug Information Services, the KP Pharmacy and Therapeutic Committees use an evidence-based approach to assess the safety and efficacy of new medications. Individual clinicians can obtain literature searches and information about new medications from the Drug Info line (available by phone in the KP Southern California Region), electronically at Drug-Info-Inquiry (available through KP e-mail), or [Drug-Info-Inquiry@kp.org](mailto:Drug-Info-Inquiry@kp.org) (accessed over the Internet).

The KP Biotechnology and Emerging Pharmaceuticals Technology Advisory Committee (BEPTAC) was formed in response to the exploding growth of new types of medication, including human proteins, mono-
Challenges to Use of New Medical Technology

Tension in evidence-based technology management is presented mostly by the statement that “there is insufficient evidence showing that this intervention is medically appropriate for patients.” Because the process tries to “stay ahead of the curve,” many assessments of medical technology initially include this statement, often reflecting existence of lag time between data collection, its presentation at specialty society meetings, and publication of the evidence in peer-reviewed medical journals. In some cases, the technology that appears in a publication is already outdated and has been replaced by newer methods. Frequently, assessments must be updated and the medical literature monitored until the technology “matures” or until high-quality investigational trials are completed.

A good current example of this sequence of events is presented by virtual colonoscopy as used for detecting polyps and colorectal cancer. The medical community eagerly awaits the results of ongoing large randomized controlled trials to determine the utility of this technology compared with standard visual colonoscopy.

Another reason for concluding that a recommendation is supported by insufficient evidence may be that different studies present conflicting evidence. In addition, other reasons may be found for recommending against use of medical technology: existing published studies may be methodologically weak or include too small a study cohort; the magnitude of the benefit may be small; or no comparison has been made with existing technologies and therefore no evidence has been presented showing that the newer technology improves upon the older technology. In these instances, one possible solution is to deploy the new technology at KP as part of a research protocol or as a quality pilot project designed to collect data for responding to unanswered questions about whether the technology deployed within KP has improved treatment outcomes. If the technology is thus deployed as part of a research protocol, we can contribute to the health of our communities also by contributing to the peer-reviewed medical literature or by publishing our own results. With our organization’s size, the interests of our clinicians, the strength of our research departments, and especially the power of an electronic medical record, the future holds much promise for us to lead in the most effective use of new medical technology.

Table 1. Recent recommendations of the KP Interregional New Technologies Committee regarding several new types of technology

<table>
<thead>
<tr>
<th>Evidence sufficient to recommend use of these technologies in selected patients</th>
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<tr>
<td>Vagal nerve stimulation for patients with intractable epilepsy</td>
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<tr>
<td>Wireless capsule endoscopy for evaluation of Crohn’s disease</td>
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<tr>
<td>Artificial lumbar disc replacement for single-level vertebral disease</td>
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<td>Bone morphogenic proteins for spinal fusion surgery</td>
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<td>Laparoscopic hysterectomy for benign uterine conditions</td>
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<tr>
<th>Evidence insufficient to recommend use of these technologies</th>
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<tr>
<td>Vagal nerve stimulation for treating depression</td>
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<tr>
<td>Electrical stimulation and electromagnetic therapy for healing of chronic wounds</td>
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<tr>
<td>Islet cell transplantation for patients with type I diabetes</td>
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<td>Robot-assisted prostatectomy</td>
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References

Update on Interventional Neuroradiology

By Amon Y Liu, MD

Introduction

Interventional neuroradiology—a relatively new medical subspecialty known also as endovascular neurosurgery—treats cerebrovascular, head and neck, and spinal disease by using minimally invasive techniques. Interventional neuroradiology was originally developed in the 1980s by neuroradiologists and neurosurgeons. Since that time, dramatic advances in interventional neuroradiology have been made possible by similarly rapid advances in medical technology, such as neuroimaging (particularly digital subtraction cerebral angiography and angiographic road-mapping), and development of revolutionary medical devices. Many medical conditions which could not be treated effectively 15 years ago can now be treated curatively using current endovascular techniques. Indeed, even within the field of interventional neuroradiology, new technology and devices introduced within the past five years have allowed interventional neuroradiologists to increase the number of life-threatening cerebrovascular diseases which can be treated effectively.

This article provides a brief overview of the historical basis for interventional neuroradiology, current treatment options for different types of cerebrovascular disease, and anticipated future developments in the field. This article also discusses current status and future plans for the Interventional Neuroradiology program at Kaiser Permanente (KP) Medical Center in Redwood City, California.

Historical Basis of Interventional Neuroradiology

Diagnostic Neuroradiology

Diagnostic neuroradiology is a subspecialty of radiology. The first report of cerebral angiography (visualization of the cerebral vascular anatomy) in a living human subject, in 1927, described a small surgical incision made in the neck to puncture the common carotid artery, after which radiopaque contrast material was injected as a bolus for serial filming of the cerebral arteries and veins. In the ensuing decades, cerebral angiography advanced considerably in accuracy, efficacy, and safety. Direct surgical incision was replaced by percutaneous direct carotid puncture, a procedure which has subsequently been supplanted by percutaneous transfemoral catheterization (ie, insertion of a catheter through the common femoral artery after percutaneous needle puncture) and use of safer radiopaque contrast materials for cerebral angiography. In addition, modern mechanical devices for injecting contrast material, advent of digital subtraction angiography, new techniques for obtaining high-speed serial films, and manufacture of modern high-performance catheters also have contributed to the evolution of cerebral angiography as an imaging modality which is safe and effective when used by experienced operators.

Concurrent with these developments, noninvasive advanced technology such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have sometimes allowed interventional neuroradiologists to make more accurate diagnoses and to plan endovascular interventions without making a skin incision to see inside the body. Further improvements in noninvasive imaging equipment and powerful computer processors have led to new techniques for visualizing the cerebral vasculature using CT or MRI. These techniques—computed tomographic angiography (CTA) and magnetic resonance angiography (MRA)—are now often used to screen patients for suspected cerebrovascular disease. These techniques reduce (but do not eliminate) the need for diagnostic cerebral angiography, which currently has greatest sensitivity for detecting subtle abnormalities or diseases of the small and distal cerebral vessels.

Interventional Neuroradiology

Interventional neuroradiology is a radiologic subspecialty which was introduced in the 1980s to help neuroradiologists and neurosurgeons to find effective techniques for treating patients for whom tradi-
tional treatments (ie, open brain surgery) were neither possible nor feasible. Conditions precluding traditional treatment included giant cerebral aneurysm, surgically inaccessible aneurysm, large arteriovenous malformation, clinically significant medical comorbidity, or a combination of these conditions. Introduction of cerebral angiography provided an avenue for achieving more effective treatment for patients with these conditions.

Through the 1980s, neurointerventional techniques were considered largely experimental and were done only for patients who had no other treatment options. In the late 1980s and early 1990s, two key developments in angiographic equipment—digital subtraction angiography and roadmap fluoroscopy imaging—permitted dramatic growth of interventional neuroradiology. Digital subtraction angiography initially had resolution inferior to that of cut-film angiography but allowed more rapid decision making during angiographic procedures by eliminating the need for using time-consuming, conventional film processing after each angiographic injection of contrast material. Roadmap fluoroscopic imaging has allowed interventional neuroradiologists to obtain angiographic images of a blood vessel, lesion (eg, cerebral aneurysm), or both by injecting only a small amount of contrast medium and to maintain this angiographic image on the fluoroscopic monitor while superimposing live fluoroscopic (x-ray) images on the angiographic image. In essence, by giving interventional neuroradiologists a “roadmap” of the angiographic image on the fluoroscopic monitor while superimposing live fluoroscopic (x-ray) images on the angiographic image, they can be deployed to treat a cerebral aneurysm. The “roadmap” also enables interventional neuroradiologists to then inflate and deploy a balloon within the aneurysm to occlude it. Indeed, interventional neuroradiology would be impossible without the advent of roadmapping.

Equally important for advancement of interventional neuroradiology were the rapid technological improvements in each successive generation of medical devices and materials. In general, therapeutic procedures in interventional neuroradiology are done through a microcatheter measuring between .013 and .021 inches in diameter. The microcatheter is inserted coaxially through a larger catheter (the “guide” catheter, measuring approximately 2 mm in diameter) placed in the groin. Under fluoroscopic (x-ray) guidance, the microcatheter is threaded through the blood vessels leading into the brain. Depending on the disease process being treated, any of several devices or materials may be deployed or injected through the microcatheter.

Despite its strong roots in the field of radiology, interventional neuroradiology has evolved into a distinct medical discipline that combines elements of radiology and neurosurgery. Emergence of interventional neuroradiology has marked a transition from the radiologist’s traditional role as a consultant: Interventional neuroradiologists serve not only as consultants but as clinicians who assume an active role and responsibility in treatment. As interventional neuroradiology continues to evolve, radiologists as well as a growing number of neurosurgeons have entered the field. The American Society of Interventional and Therapeutic Neuroradiology was formed in 1992 as the governing body for this multidisciplinary field.

**Current Treatment Options in Interventional Neuroradiology**

The minimally invasive procedures used by interventional neuroradiologists accomplish a wide variety of treatments (some of which are described in this article) designed to provide pain relief as well as to correct life-threatening conditions. Such conditions include aneurysm (treated by inserting platinum coils into the aneurysm bulge to promote clotting and to prevent rupture), abnormal, enlarged cerebral arteries (treated by injecting embolic material into an arteriovenous malformation to prevent life-threatening hemorrhage), and stroke (treated either by delivering “clot-busting” drugs directly to the site of blockage or by using microdevices specifically designed to retrieve clots). As alternatives to invasive surgery, these forms of therapy are often advantageous because they can lower the risk to patients, shorten hospital stays, and hasten recovery. Endovascular techniques also allow treatment of many lesions which could not be treated with open surgery.

Similarly, interventional neuroradiologists use endovascular and other percutaneous techniques to treat some types of head and neck disease (for example, embolic or sclerosing agents are injected to treat carotid
Special Feature

The Neuroform stent (Boston Scientific, Natick, MA) facilitates treatment of wide-necked cerebral aneurysms by bridging the neck of the aneurysm with a very thin meshwork which prevents coil loops from prolapsing into the parent vessel and thereby reduces the risk of a treatment-related stroke.

Treatment of Cerebral Aneurysms

Initially, only aneurysms described as giant (> 2.5 cm) or otherwise inoperable were treated using endovascular techniques. These aneurysms were treated by inflating and detaching small silicone or latex balloons within the aneurysm in the hope that filling the aneurysm would prevent its rupture. Other aneurysms were treated, where possible, by using balloons to deliberately occlude the blood vessel both proximal and distal to the aneurysm.

The early 1990s brought a revolutionary advance to interventional neuroradiology: the Guglielmi Detachable Coil, GDC (Boston Scientific, Natick, MA). This device is an electrolytically detachable platinum coil which can be delivered into a cerebral aneurysm to promote clotting within the aneurysm. If satisfactory positioning of the coil cannot be achieved, it can be withdrawn through the microcatheter. Currently, interventional neuroradiologists planning treatment of aneurysms can choose from among several types of FDA-approved coils: bare platinum coils, 2- and 3-dimensional coils, aneurysm-conforming coils, bioactive coils, and hydrogel-coated coils. These coils differ from one another in performance characteristics, advantages, and disadvantages. When used in the appropriate setting, these newer-generation coils are expected to improve the stability of aneurysm coiling and thereby reduce the need for repeat embolization.

The International Subarachnoid Aneurysm Trial (ISAT) was designed to compare the efficacy of aneurysm coiling versus open surgery in patients with ruptured aneurysms. In 2002, investigators showed that patients who were treated with coil embolization had improved outcomes compared with patients who received open surgery.

The next revolutionary advance in endovascular treatment of cerebral aneurysms came in 2003 with the introduction of the first stent approved by the FDA for intracranial use. The Neuroform stent (Boston Scientific, Natick, MA) facilitates treatment of wide-necked cerebral aneurysms by bridging the neck of the aneurysm with a very thin meshwork which prevents coil loops from prolapsing into the parent vessel and thereby reduces the risk of a treatment-related stroke.

Treatment of Cerebral Vasospasm

Interventional neuroradiologists are also frequently called upon to treat cerebral vasospasm, one of the devastating sequelae of aneurysmal subarachnoid hemorrhage. Endovascular treatment of vasospasm may include use of a microcatheter for intraarterial injection of vasodilating agents, or balloon angioplasty of the intracranial vessels.

Treatment of Cerebral Arteriovenous Malformations and Dural Arteriovenous Fistulae

These types of vascular malformations can often cause debilitating symptoms such as headaches or pulsatile tinnitus (“ringing or buzzing in the ears”) and can cause life-threatening intracranial hemorrhage. Depending on the type of arteriovenous vascular malformation involved, interventional neuroradiologists can very effectively treat these lesions by injecting embolic agents such as polyvinyl alcohol (PVA) and n-butyl cyanoacrylate (colloquially known as “glue” and approved by the FDA in 2003) into arteries supplying the lesions. In August 2005, the FDA approved Onyx (Micro Therapeutics, Irvine, CA), a nonadhesive liquid embolic system composed of ethylvinyl alcohol dissolved in dimethyl sulfoxide, for preoperative and radiosurgical embolization of arteriovenous malformations. Other types of vascular malformation can be treated using platinum coils placed through a transvenous approach.

Treatment of Intracranial and Extracranial Atherosclerosis

Increasingly, interventional neuroradiologists are also treating these conditions by using endovascular techniques, such as balloon angioplasty, stenting, or both techniques. In patients who have symptomatic intracranial atherosclerosis and who have suboptimal results of medical management using antiplatelet agents or anticoagulants, stroke is highly likely to develop shortly after this medical treatment; in such cases, use of intracranial angioplasty, stenting, or a combination of these techniques can make the disease less debilitating by improving cerebral perfusion, by reducing the risk of thrombotic/embolic events, or by both actions. The FDA has recently approved the first intracranial stent, the Wingspan (Boston Scientific, Natick, MA), for use in atherosclerotic disease, further raising the prospects for improved outcomes in affected patients. Stenting of the extracranial carotid and vertebral arteries has also advanced greatly. Carotid endarterectomy done by an experienced surgeon remains a highly effective
method of treating symptomatic carotid stenosis, and most interventional neuroradiologists reserve stenting for patients who are poor candidates for carotid endarterectomy. In these patients, the procedure is precluded by recurrent postendarterectomy stenosis, radiation-induced stenosis contralateral carotid occlusion, high-cervical stenosis, or clinically significant medical comorbidity. However, multicenter randomized clinical trials, such as the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST), are well underway to determine whether carotid stenting done by experienced operators is superior, equivalent, or inferior to endarterectomy for treating carotid stenosis. Early results of this study have been encouraging for stenting.

Vertebroplasty
In many cases, painful spinal compression fracture (osteoporotic or traumatic), isolated vertebral bone metastasis, and vertebral hemangioma can be treated effectively with vertebroplasty when the pain is not relieved by analgesic medications. In such cases, a large spinal needle is guided percutaneously into the fractured bone under x-ray guidance, and a bone cement mixture is then carefully injected into the bone to treat the fracture. In approximately 90% of appropriately selected patients, the pain is either partially or completely relieved after completion of this procedure. Many patients who receive the procedure can safely eliminate or substantially reduce their use of pain medication.

Future Developments in Interventional Neuroradiology
The rapid pace of technological innovation in interventional neuroradiology makes this a very exciting field. Although we cannot precisely predict what new devices may become available in the next five years, we can certainly expect continued improvement in successive generations of the coils and stents used for treating aneurysms. The Onyx liquid embolic system (Micro Therapeutics, Irvine, CA) has also been used successfully in clinical trials to treat selected cerebral aneurysms, and the manufacturer is expected to seek FDA approval for this indication within the next two to three years. This embolic material may ultimately be used in conjunction with coils or may in some cases replace use of coils for aneurysm treatment.

In August 2004, endovascular treatment of acute ischemic stroke was advanced substantially by FDA approval of the Merci Retriever device (Concentric Medical, Mountain View, CA). The device is designed to restore flow to the brain by retrieving embolic material (or blood clot) within an occluded cerebral vessel. Nonetheless, the device is only approximately 50% effective in appropriately selected patients. Further improvement in this and other similar devices is anticipated.

Continuing improvement in imaging technology is also expected to enhance the capabilities of interventional neuroradiologists. Angiographic equipment improvements in image resolution, 3-D imaging, and imaging of soft tissue all will help interventional neuroradiologists to make more effective treatment decisions.

The Interventional Neuroradiology Program at the KP Redwood City Medical Center
The Interventional Neuroradiology program at the KP Redwood City Medical Center is led by Amon Y Liu, MD; Gwinette Cowan, RN (Manager, Interventional Services); and Beverly Land, RN (Interventional Neuroradiology Nurse Coordinator) and includes a team of six angiography technologists and five staff nurses. In September 2005, the team was joined by a second neurointerventionalist, Sean P Cullen, MD.

The goals of the Interventional Neuroradiology program at the KP Redwood City Medical Center are

- to extend the range of cerebrovascular and head and neck diseases that can be effectively treated;
- to improve rates of morbidity and mortality associated with treating cerebrovascular and head and neck disease; and
- to improve continuity of care and to reduce treatment delays in the KP Northern California Region.

As the regional service center for the neurosciences, the KP Redwood City Medical Center has been able to form this cohesive team, which uses a multidisciplinary approach to treating patients diagnosed with neurological disease. With regard to patients with cerebrovascular disease in particular, specialists in interventional neuroradiology, neurosurgery, and neurology-critical care work closely with each patient to determine the best course of treatment and management. At present, the Interventional Neuroradiology service can provide all FDA-approved treatments that do not require participation in clinical trials (except treatments for acute ischemic stroke, which are treated on a case-by-case basis). Participation in selected clinical trials is considered if a potential benefit to a patient can be established. The service expects to offer complete coverage for acute ischemic stroke upon certification by the American Stroke Association as a comprehensive stroke center.
References


Suggested Reading
• Rosenwasser RH, editor. Neurosurg Clin N Am 2000 Jan;11(1) [entire issue].

The Mysterious

The most beautiful thing we can experience is the mysterious. It is the source of all true art and science.

—Albert Einstein, 1879-1955, physicist, 1921 Nobel Laureate in Physics
Implementation of a Teleradiology System to Improve After-Hours Radiology Services in Kaiser Permanente Southern California

Abstract
Kaiser Permanente Southern California (KPSC) has implemented a teleradiology service to provide after-hours radiology services to its 11 medical centers from 7:00 pm to 7:00 am each day of the week. Features of the service include a Web application that is used to manage the workflow associated with teleradiology exams and to provide reports of the teleradiologists’ findings to referring clinicians. Currently, two teleradiologists who can be located at any KPSC facility (varies from day to day) are used to provide preliminary interpretations of CT, MRI and ultrasound exams. However, the service is scalable and could be easily reconfigured to accommodate additional teleradiologists if needed. The service also includes a quality monitoring system that tracks significant discrepancies between the teleradiologist’s findings and the subsequent final report of a medical center’s staff radiologist. Clinicians who utilize the teleradiology service have been highly satisfied with the responsiveness of the service—median time between performance of an exam and availability of a wet read is 19 minutes.

For several years, the Southern California Chiefs of Radiology explored various technology options to improve the efficiency of after-hours services. Until 2002, on-call radiologists at each of the 11 medical centers provided after-hours radiology services for their local Emergency Departments (ED) in Kaiser Permanente Southern California (KPSC). This process had been in place for many years and reflected the medical group’s political structure (essentially 11 separate groups of radiologists). The time lag between when a radiologist received a page and when s/he arrived at the medical center produced inevitable delays in providing radiology consultations to EDs. In most cases, the radiologist was needed only to provide image interpretation, not to perform the exam.

The Chiefs discussed a variety of options, including providing each on-call radiologist with the ability to view exams and transmit interpretations from home. This and other potential solutions did not prove to be feasible for various reasons, including: concern over the quality of images viewed on home computers, the challenge of remotely supporting a variety of home systems and the Southern California Permanente Medical Group compensation structure. After much discussion, the Chiefs, with the support of administration, elected to implement a teleradiology system that would station a radiologist in a central location to provide image interpretation for CT, MRI and ultrasound exams from 7:00 pm to 7:00 am seven days a week for all KP Southern California medical centers. “Wet read” reports would be communicated via fax to the referring ED.

However, when working out the final details of the implementation, two important changes were made. First, the single central location plan was abandoned. The radiologists strongly preferred an alternative option that provided the ability to access the teleradiology studies from any of KPSC’s 11 medical centers. This alternative permitted each teleradiologist to work from his/her home medical center, or another if more convenient. This change was made due to concerns about the willingness of radiologists interested in working a teleradiology shift to...
travel to a central location (for example radiologists who normally worked in San Diego to travel more than 125 miles to Pasadena). Doing so offered the advantage of having the teleradiologist work in a familiar setting, using familiar equipment and traveling no more than for a typical workday. Second, the plan to communicate the teleradiologist’s findings via fax was replaced by a Web application that would provide the ability to track a request for teleradiology services throughout the entire process, as well as communicate the findings to the referring site.

Workflow

Two different components of teleradiology needed to be managed as part of the workflow (Figure 1): information and images. Information workflow begins with the ED initiating a request for an exam. Required information during this first step includes the patient’s name, medical record number, date of birth, clinical reason for the exam, radiology exam requested, and name and contact information of the clinician who needs the results. Next, a radiologic technologist performs the requested exam. At the completion of the exam, the technologist can add comments to the information record that could be useful to a radiologist interpreting the exam (eg, technologist’s impressions during an ultrasound exam are particularly helpful to radiologists remotely reading the resulting images). The technologist documents that the exam has been performed and the images sent to the teleradiologist. Step three is the teleradiologist reading the exam and documenting his/her preliminary findings (“wet read”). The Web application makes these available to the referring site where the clinician or staff, who originally requested the exam, views the findings as the fourth step. Any user can view the up-to-date status for each exam (requested, performed, read). In addition, the Web application alerts teleradiology support staff when the referring site has not accessed the interpretation after 30 minutes so that they can follow-up with the site.

Images are the second component of the teleradiology workflow. Images produced during an exam need to be delivered to the teleradiologist for interpretation. Because the location of the teleradiologist varies from day to day, there was concern that images could be frequently misrouted to the wrong location if technologists had to check schedules and send the completed exam’s images directly to the teleradiologist. This design would also have required that each possible teleradiologist location (at least 11 sites) be configured on each of the 50+ possible imaging systems used for the exams. For these reasons, a central image router serving all of Southern California was installed. Exam images are communicated via Digital Imaging and Communications in Medicine (DICOM) from the originating imaging system (eg CT scanner) to the router. DICOM is a non-proprietary industry standard for communicating images in digital form between medical devices. The router then automatically sends the images directly to the workstation at the location of the teleradiologist for that day. Changes in teleradiologist location are easily accommodated by changing the destination configuration of the router.

Initial Launch, Expansion and Scalability

EDs in 5 of the 11 medical centers in Southern California were included in a pilot of the teleradiology service in August 2002 so that the process could be refined before expanding the service to the entire Region. As the remaining six medical centers were brought online, the workload grew to the point that a single teleradiologist was no longer sufficient. Furthermore, although originally designed to support the EDs, workload increased substantially due to addition of urgent after-hours inpatient and some outpatient studies. The design flexibility of both the image router and the Web application accommodated this increase in workload with the addition of a teleradiologist.
In this expanded model, the Region was divided into two groups, with a teleradiologist assigned to each group. Medical centers were assigned to a group on the basis of their historical workload so that the total workload for each group would be roughly equal. This method of balancing the workload among teleradiologists also insured that multiple exams performed on the same patient during a shift would be read by the same teleradiologist. The image router sends the exam to the workstation of the appropriate teleradiologist on the basis of knowledge of the medical center from which the exam was submitted. Consequently, each teleradiologist only sees a worklist of the exams requested by the medical centers in his/her group.

The ability to have multiple groupings for workload division and to route images on the basis of their source allows the teleradiology service to expand as workload grows in the future and more teleradiologists are needed. The design will also support variable shift schedules should these be developed.

Monitoring Quality

One of the concerns that surfaced during the development of the teleradiology service was how to monitor the quality of the teleradiologists’ findings when the teleradiologist was, in most cases, providing preliminary reads of exams originating from medical centers other than his/her own. To address this issue, the Web application used to support the exam workflow was enhanced to include a post-exam quality monitoring process. Since the teleradiology findings are only “wet reads,” all teleradiology exams are subsequently interpreted by a staff radiologist at the originating medical center. The local staff radiologist’s interpretation is the official diagnostic report for the exam. This practice is identical to that used for any preliminary interpretation.

The first step in the quality monitoring process is comparison by the staff radiologist of the teleradiologist’s preliminary findings with his/her official diagnosis for the same exam. The staff radiologist uses the Web application to enter whether there was a significant difference in findings and to add any pertinent comments.

The designated QA radiologist for each medical center performs the second step in the process. This radiologist reviews each exam noted to have a significant difference in interpretation between the teleradiologist and staff radiologist. The QA radiologist also uses the Web application to enter whether s/he agrees that a significant difference in findings exists and to record pertinent comments.

The third process step is performed by four radiologists who meet quarterly to collectively review those teleradiology exams for which both the interpreting staff radiologist and the medical center’s QA radiologist agreed there was a significant difference from the teleradiologist findings. The conclusions of this group of four are recorded in the Web application and the teleradiologist is notified of any exam for which the group agreed there was a significant difference between the group’s findings after reviewing the actual images and the original teleradiology findings. Quality statistics for each teleradiologist are maintained in this fashion for all exams.

Staff Support

During each teleradiology shift, regional staff is on duty and immediately available via telephone to support the teleradiology workflow. Typically, requested support consists of determining the cause of any delays that may occur in performing or interpreting requested exams and following-up on exams with completed findings that have not been viewed by the requesting department within a reasonable amount of time. The goal is to assure that clinicians are aware of the teleradiologist’s findings. This staff is also responsible for implement-

### Sidebar: Teleradiology statistics

Statistics for the six months of teleradiology activity from March 1 to August 31, 2005:
- Average number of exams per 12-hour shift: 125
- Annualized number of exams per year: 46,000
- Number of teleradiologists per shift: 2

Proportion of exams by imaging modality:
- CT: 80%
- Ultrasound: 19%
- MRI: 1%

Proportion of teleradiology requests by referring department:
- ED: 85%
- Outpatient: 9%
- Inpatient: 6%

Median delay from exam performed to teleradiologist wet read: 0:19 (hrs:min)
Median delay from exam requested to teleradiologist wet read: 1:17 (hrs:min)
Busiest teleradiology hours (based on time read): 8:00 PM to midnight (50% of exams)
ing a manual method of communicating teleradiology results if the Web application fails. In the event of technical problems with the Web application or with the image router, staff can contact on-call imaging technical support staff.

Regional staff support the quality monitoring process and collect the images for the exams that need to be reviewed for the third process step, compile the group’s findings and provide communications of the findings to teleradiologists.

**Future Directions**

As the teleradiology workload increases, methods to incrementally increase capacity in an efficient manner continue to be investigated. Rather than simply adding another teleradiologist for an entire 12-hour shift, it may be advantageous to add teleradiologist capacity only during the peak hours of activity (see sidebar: Teleradiology Statistics). For example, three teleradiologists could be scheduled for the first half of the shift and two for the remainder of the shift.

Another process improvement under investigation is provision of the complete official diagnostic findings by the teleradiologist, rather than only reporting preliminary findings as is currently the case. Several operational and technical challenges will need to be adequately addressed in order to implement this change in teleradiology practice: a) teleradiologist staffing will need to be adjusted to allow for the longer interpretation times required for final reports as compared to preliminary findings; b) conversion of the imaging modalities to a filmless environment will need to be complete across the Region in order to support efficient retrieval of prior exams required to support final reports; and c) the dictation/transcription process for radiology reports will need to be modified to accommodate any radiologist providing a report for any medical center from any location.

**Conclusion**

The KPSC teleradiology service has improved Radiology’s support of EDs by significantly decreasing delays in providing after-hours interpretation of CT, MRI, and ultrasound exams. The Chiefs of Emergency Medicine have been enthusiastic about the prompt service that minimizes the time required for clinical management decisions in EDs, enhances throughput and helps improve ED capacity. The service has also made it possible to more effectively manage the Region’s collective radiologist resources and to provide a process to assure the ongoing quality of those services—developments that have produced a high level of confidence in the results among emergency physicians. In addition, radiologists have experienced an improved quality of life due to the significant reduction of “callbacks” when on call for their medical centers.

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**To Win**

Pick battles big enough to matter, small enough to win.

—Jonathan Kozol, b 1936, non-fiction writer, educator, and activist