

Five decades of  
**DISCOVERY**

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2012 Annual Report

# Creating New Knowledge for Our Patients and for Society



My colleagues and I in the Division of Research have the distinct privilege of working with patients and clinicians in a real-life, integrated health care system. Morrie Collen, a founding father of Kaiser Permanente, created our research group in 1961 to do studies that benefit our own patients and society at large.

As we celebrated our 50th anniversary last year, we reflected on our robust history of collaborating with clinicians and program leaders to produce research that transforms health.

Our cancer research is a case in point. Our work in this important field spans the complete spectrum of research with patients. For example, in colorectal cancer and breast cancer we are studying genetic, environmental, and other causes of the disease; working on methods to enhance early detection; and evaluating the effectiveness of clinical options for affected patients. The breadth of this work shows the tremendous power of our integrated health care system to foster top-quality research.



Last year, we focused concerted attention on laying the foundation for our Division's future. After my arrival as the new Director, our research scientists and I updated our scientific organizational structure. We have clustered into six scientific sections — Behavioral Health and Aging, Cancer, Cardiovascular and Metabolic Conditions, Health Care Delivery and Policy, Infectious Diseases, and Women's and Children's Health — and a Biostatistics Core. We look forward to this new structure enhancing scientific dialogue among collaborators within and outside our Division.

We have initiated a new portfolio in delivery science, which studies ways of providing effective health care to diverse patients in actual practice. With support from The Permanente Medical Group, we are starting new projects in high-priority areas designed to yield results that directly affect how we design our health care programs. For example, the medical group has identified the care of patients with complex chronic conditions as a domain where our research can contribute new insights, and we are initiating new work in this important area. We are also planning a Delivery Science Fellowship Program to develop young scientists with the methodological skills, experience, and perspective to expand our capacity in this type of research.

Our research group is well-positioned for continued growth, but we also face challenges. Approximately four-fifths of our Division's funding comes from external sponsors, including the National Institutes of Health and other federal agencies, foundations, and industry. Our researchers compete for external grants and contracts, and while we have been highly successful, the national funding environment is tight and is likely to remain so for the next five years. We are continually shaping our research portfolio to leverage our existing resources, position ourselves to make contributions that are unique, and conduct projects that are both innovative and high impact.

We are extremely grateful for the moral and financial support of our many collaborators and sponsors among the clinicians and program leaders of The Permanente Medical Group, Kaiser Foundation Health Plan, and Kaiser Foundation Hospitals. This support — as well as the dedicated and creative effort of all our scientists and staff members — promotes the innovation, collaboration, and ultimate impact of the top-notch work our research teams accomplish on a daily basis.

On behalf of everyone in our Division of Research, I extend our sincere appreciation for your engagement in our groundbreaking efforts to enhance health and health care.

Tracy Lieu, MD, MPH  
Director, Division of Research  
Kaiser Permanente Northern California





## Behavioral Health and Aging

Many components of total health converge in Behavioral Health and Aging. Research methods include genome-wide association studies, epidemiology, clinical, comparative effectiveness, cost effectiveness, and other health services research.

Research topics include individual health conditions, but also foster connections across behavioral and mental health, including: alcohol and drug studies; chronic pain and prescription drug abuse; innovative models of care for alcohol, drugs, depression, and bipolar disorder; behavioral health and violence prevention; metabolic, cardiovascular, and inflammatory predictors of cognitive aging and dementia; physical activity and healthy aging; and clinical trial methodology for alternative and complementary medicine and therapies.

### Primary Research Areas

- ▶ Access and utilization of behavioral health care
- ▶ Alcohol and drug epidemiology, early intervention and treatment trajectories
- ▶ Alzheimer risk factors and metabolic predictors of cognitive impairment
- ▶ Chronic pain and prescription drug abuse
- ▶ Complementary and alternative medicine
- ▶ Depression and bipolar disorder
- ▶ Exercise and women's health
- ▶ Genetics, environment, and health
- ▶ Internet-based treatment
- ▶ Physical activity and cancer
- ▶ Physical activity, function, and aging

## Alcohol Screening Joins List of Vital Signs



**According to the *American Journal of Preventive Medicine*, alcohol screening and brief intervention is ranked fourth of 25 preventive primary-care services — above screening for hypertension, diabetes, cholesterol, and depression — for improving health and lowering health care costs.**

Yet this screening for unhealthy drinkers has not been widely adopted by primary care practices in the United States.

Addressing alcohol use in primary care has an impact on many key health problems. For the 7.5 percent of patients who drink at unhealthy levels, it increases their risks for cancer, hypertension, diabetes, depression, sleep disorders, and falls and other injuries, and is linked to medication noncompliance. Ninety percent of these patients do not have alcohol dependence, and a brief intervention in primary care can reduce their alcohol consumption to a low-risk level. In addition, it can help the smaller group of patients (about 0.7%) who do have alcohol dependence to access specialty treatment.

In 2010, with a grant from the National Institute on Alcohol Abuse and Alcoholism, researchers in the Behavioral Health section began a study on the optimal model for implementing and sustaining a program of screening, brief intervention, and referral to treatment (SBIRT) for unhealthy drinkers.

A major challenge of the study was to understand the barriers to implementation, which include lack of awareness as to what amount of alcohol consumption constitutes low-risk drinking, the perceived sensitive nature of the topic, and the many competing priorities physicians have in a primary care setting.

Researchers randomly assigned 54 clinics in 11 medical centers to these three approaches, to learn not only which of the approaches is more likely to be implemented, but also which one is most sustainable.

A key finding for both implementation and sustainability of the workflow is “keep it simple.” Medical assistants are automatically prompted by an electronic program to ask patients a few simple questions about alcohol consumption. When patients screen positive through answers that indicate they are above the low-risk limits, an alert lets the physician know that a conversation is needed. That conversation is a natural progression of noting the patient’s alcohol consumption level, explaining the effects it can have on their health, making them aware of low-risk levels, and asking them if they are willing to cut back.





## Cancer

Kaiser Permanente Northern California has approximately 20,000 new cancers diagnosed each year, and the membership includes over 200,000 cancer survivors. Our high-quality tumor registry — together with electronic databases and hard-copy records — provide unparalleled opportunities for studying cancer etiology and prevention, screening, diagnosis, treatment, and survival. Our research includes the role of nutrition, lifestyle, and environmental factors on cancer incidence and prognosis, and gene expression and molecular factors in cancer diagnostics and outcome prediction.

We study a broad range of cancers, with a major focus on cancers of the breast, prostate, and gastrointestinal tract, as well as the skin and lung. Our researchers have major leadership roles in large collaborative efforts, including the National Cancer Institute's Cancer Research Network, the Women's Health Initiative, and the colorectal cancer component of PROSPR (a national cancer screening study).

### Primary Research Areas

- ▶ Breast cancer etiology, progression, and survivorship
- ▶ Prostate cancer etiology and progression
- ▶ Skin cancer epidemiology and prevention
- ▶ Genetic determinants of cancer
- ▶ Nutrition and lifestyle factors
- ▶ Biomarkers and diagnostics in breast, prostate, and lung cancer
- ▶ Medications and cancer risk
- ▶ Social networks and breast cancer survivorship
- ▶ Determinants of early puberty in girls
- ▶ Long-term effects of cancer treatment
- ▶ Genetic and environmental risk factors for gastrointestinal cancers
- ▶ Evaluation of screening methods for gastrointestinal cancers

# Pioneering Research Takes Colorectal Cancer Screening to the Next Level



## **The Kaiser Permanente Division of Research has been an indisputable innovator in the science of screening for colorectal cancer.**

Studies by our scientists have contributed to national screenings guidelines, while delivering the most effective methods to Kaiser Permanente members and the community.

More than 142,000 new cases of colorectal cancer are diagnosed in the United States each year, and these cancers cause about 50,000 deaths. Many of these cancers are preventable with screening and early detection.

Now, a five-year, \$5.7 million study funded by the National Cancer Institute (NCI) is providing researchers in the Cancer section with the opportunity to investigate why some colorectal cancers are still missed by screening and to develop science-based improvements in the methodology.

NCI's PROSPR program has funded seven research centers around the United States to examine screening for breast, cervical, and colorectal cancer. With 2 million members of screening age in California, Kaiser Permanente offers one of the largest resources of its kind for studying colorectal cancer screening.

Kaiser Permanente recommends that all its members over age 50 have colorectal cancer screening with one of three options: annual fecal immunochemical tests (FIT), a sigmoidoscopy every five years, or a colonoscopy every 10 years.

Annual FIT testing and intermittent colonoscopy are approximately equally effective at preventing deaths from colorectal cancer. FIT has the added benefits of being noninvasive, not requiring a bowel preparation or sedation, and having virtually no risk of complications.

With HealthConnect (Kaiser Permanente's comprehensive electronic medical record), DOR researchers are able to link colorectal cancer screening results with a host of other demographic and medical factors to get an even clearer picture of what is working with our screening program and how it can be improved.

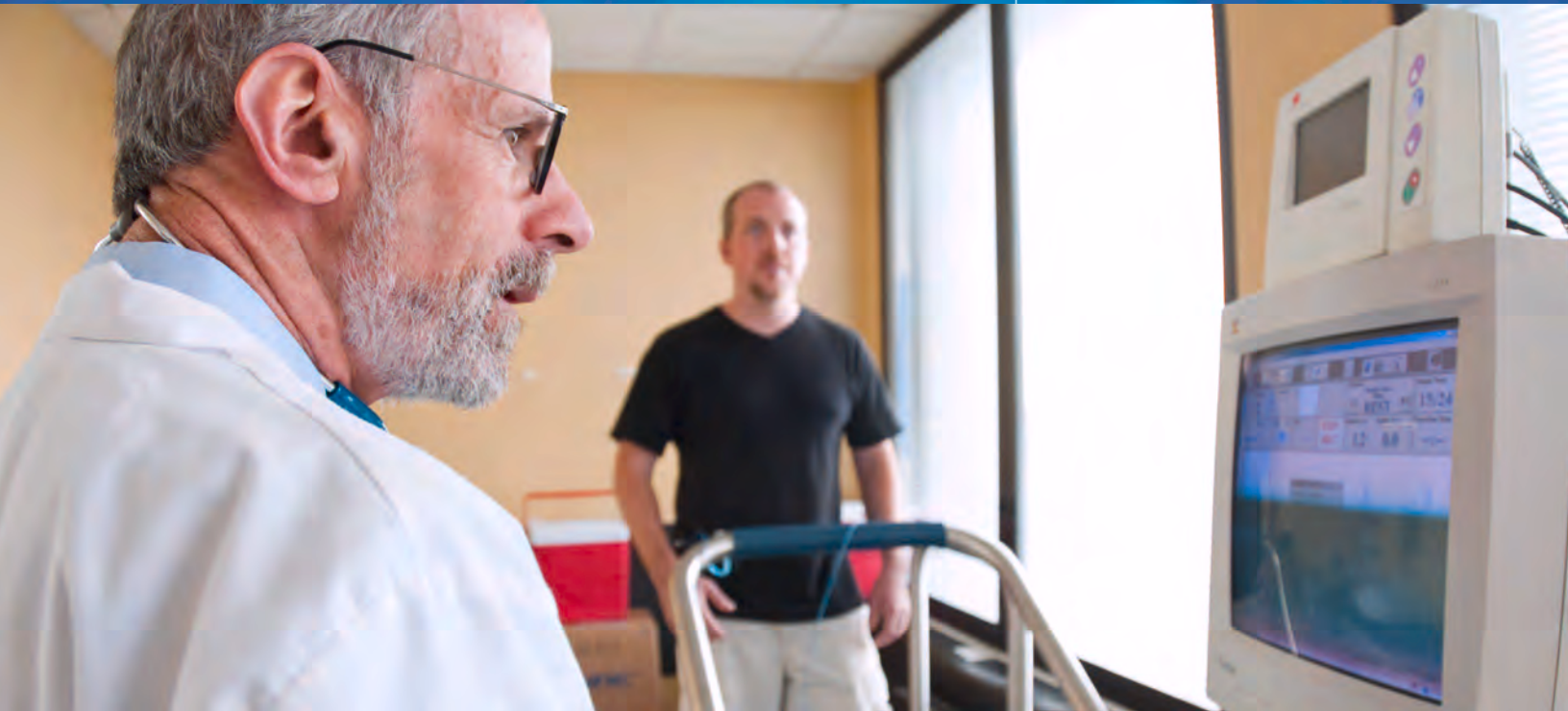
In year two, the PROSPR study has already yielded some important insights.

First, adherence rates for Kaiser Permanente's recommended annual FIT screenings are high, and the screenings are working. While about 50% of the U.S. population is screened, more than 85% of California Kaiser Permanente members were adequately screened over a five-year period. Of those diagnosed with colorectal cancer, the FIT screening found 73% and 80% of the cases in two separate cohorts.

Second, researchers have found that the detection of adenomas, the benign tumors that are precursors to colorectal cancer, is associated with the patient's subsequent risk of cancer.

The next step in the study will be to conduct a systematic evaluation of the whole process of doing a colon exam, in order to optimize the results and potentially decrease future cancers and cancer deaths.





## Cardiovascular and Metabolic Conditions

Cardiovascular research is a major emphasis at the Division of Research. Through studies, such as Coronary Artery Risk Development in Young Adults (CARDIA), and multi-institutional partnerships including the Cardiovascular Research Network (CVRN), investigators study the epidemiology, prevention, management, and outcomes of cardiovascular diseases, including cerebrovascular and peripheral vascular conditions.

Research in metabolic conditions informs the prevention and treatment of disease throughout the course of life, as events such as pregnancy and the process of aging affect the body's major systems. Active areas of investigation include the prevention and treatment of acute and chronic kidney disease, endocrinologic conditions related to women's health, and social determinants of health.

### Primary Research Areas

- ▶ Acute and chronic heart failure
- ▶ Acute and chronic kidney disease and associated clinical complications
- ▶ Atrial fibrillation and stroke prevention
- ▶ Cardiovascular health services research and clinical epidemiology
- ▶ Cardiovascular pharmacoepidemiology and pharmacogenomics
- ▶ Cerebrovascular disease epidemiology and outcomes
- ▶ Gestational diabetes mellitus: long-term effects on women's health
- ▶ Inflammation and endothelial function
- ▶ Osteoporosis
- ▶ Pregnancy-related complications and clinical outcomes
- ▶ Vascular imaging and clinical complications



## A New Risk Assessment Tool Predicts Stroke in Atrial Fibrillation



**The focus of the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study has been to evaluate the risks and benefits of warfarin treatment, and to give patients and physicians quantitative guidance in making therapeutic decisions for stroke prevention.**

Atrial fibrillation affects more than 2.3 million Americans. Because the heart rhythm disturbance promotes the formation of blood clots that can travel to the brain and block an artery, atrial fibrillation independently increases the risk of ischemic stroke four-to-five-fold. The condition is highly age-dependent and affects 10 percent of those over age 80.

Researchers have long known that warfarin, a blood-thinner and anticoagulant, is highly effective in preventing such strokes, but treatment can be difficult to control and often leads to hemorrhage. Balancing the benefits of warfarin against its most severe risks is critical to making the best therapeutic decisions for individual atrial fibrillation patients. The current risk assessment formulas recommended by leading clinical practice guidelines have only moderate ability to predict which patients will have a stroke.

More accurate, reliable, stroke risk-prediction tools are needed to optimize anticoagulation decision-making for patients with atrial fibrillation. Now ATRIA study researchers have developed a new stroke prediction model using the original ATRIA cohort, and externally validated the score in a separate contemporary cohort drawn from partner organizations in the CVRN, which is sponsored by the National Heart, Lung, and Blood Institute.

Researchers used the large observational follow-up of the original ATRIA cohort members not taking warfarin to optimize the use of common clinical features to predict stroke risk. They validated the core risk factors used in the existing risk score but added features that they have previously reported to predict stroke — female sex, renal dysfunction, and excess urinary protein excretion.

ATRIA researchers also used a broader range of age categories, a decision consistent with multiple prior reports. They found strong amplification of stroke risk across the entire age range, with individuals greater than 85 years old at nearly double the risk of those aged 75 to 84 years. However, individuals who had had a prior stroke were at elevated risk regardless of age. Age, prior stroke, and their interaction proved to be the dominant risk factors.

The ATRIA Risk Score performed better among ATRIA cohort members than the existing risk schemes. More patients were accurately classified as low or high risk for ischemic stroke. Indeed, 46 percent of patients in both cohorts were categorized by the ATRIA score as having less than a 1 percent per year risk. Such low risk indicates a small net benefit from anticoagulation therapy.



## Health Care Delivery and Policy

Investigators in this section are committed to population-based research aimed at improving member and community health, health care delivery and the quality of care; managing health care costs; and maximizing the capacity of health care systems to address pressing public health priorities. Working closely with clinical and operations leaders, we study patient quality improvement, health care disparities, medical ethics, chronic disease management, health information technology, patient safety, and implementation research.

Leveraging rich electronic data resources, we conduct clinical trials, observational and longitudinal data analysis, survey research, simulations, and pharmacoepidemiology studies, and employ other rigorous and novel methodologies. Our investigators are particularly interested in exploring how to better serve vulnerable populations — such as children, low-income people, minorities, and hospitalized patients — and identifying opportunities for health system improvement.

### Primary Research Areas

- Health plans and insurance
- Chronic disease care and outcomes
- Health care disparities and barriers to care
- Hospital processes, outcomes, and critical care
- Health services and effectiveness
- Patient education and health promotion
- Health information technology
- Predictive modeling

# Alert System Seeks to Prevent In-Hospital Patient Deteriorations



**A new alert system under development by Division of Research scientists seeks to identify patients at risk of in-hospital transfers to the intensive care unit (ICU).**

About one in five patients transferred within a hospital dies, and research has shown that about 10% of those transfers are preventable. Likewise, most such events occur within 48 hours of entering the hospital.

Because of efforts to reduce routine hospitalization, people admitted to the hospital are generally much sicker than they were in the past. But just how sick they are is sometimes difficult for doctors and hospital staff to assess. Most can easily distinguish between the very sick and the healthy, but evaluating that in-between group of patients at risk of in-hospital ICU transfer is much more difficult, especially for physicians without decades of clinical experience and intuition.

New research being conducted in the Health Care Delivery and Policy section focuses on developing a probabilistic alert that will accurately predict a patient's risk of physiologic deterioration within a narrow time frame of 10 to 12 hours, so that action can be taken to prevent further decline.

Alerts are common in the hospital setting. Some alerts are simple reminders that, for example, point out dosage errors or potentially dangerous interactions between medications.

Rather than pointing out potential errors, probabilistic alerts generate a risk estimate for all patients in a given category — in this case, a general hospital ward. This type of alert involves computer analysis of multiple weighted factors, using complex algorithms. Clinicians can then decide what threshold will be used for actually sounding an alarm.

Called EDIP (Early Detection of Impending Physiologic deterioration), the new alert uses a mathematical model that is an order of magnitude more complicated than hospital alerts commonly in use today. It analyzes several dozen factors that are already charted in HealthConnect (Kaiser Permanente's electronic medical record), including lab tests, vital signs, and trends in vital signs, and lets physicians know which patients are at greatest risk of having an unplanned transfer.

Researchers and clinical leaders have recommended that the alert system's usability for physicians be evaluated before wider use. EDIP is currently being reviewed and tested at the Division of Research and in South San Francisco, and could be in full use there by late 2013.





## Infectious Diseases

Investigators in the Division of Research have a long history in the study of emerging and chronic infections, such as seminal work in human papillomaviruses (HPV) and their link to cervical cancer. Other major research concentrations of the section include the treatment, care, and outcomes for patients with HIV/AIDS, chronic hepatitis B (HBV), and hepatitis C (HCV).

Specific research topics have included the relationship between chronic infection and a range of cancers; studies of disease transmission from animals to humans; and the evaluation of disparities in infectious disease incidence and outcomes by race/ethnicity, age, and other factors. The section also has broad research experience with other infections, such as influenza virus complications and hospital-borne infections. In addition, it advances scientific understanding of vaccines in all levels of development through the Vaccine Study Center.

### Primary Research Areas

- ▶ Behavioral interventions in HIV-positive patients
- ▶ Epidemiology and management of viral hepatitis B and C
- ▶ HIV/AIDS epidemiology, treatment, and outcomes
- ▶ HIV-associated comorbidity in older patients
- ▶ Infectious diseases at the interfaces between wildlife, domestic animals, and humans
- ▶ Racial and ethnic disparities in health care and outcomes for chronic viral infections
- ▶ Trends in the incidence and underlying causes of liver cancer
- ▶ Virus-related cancer prevention and control

# Patient Perspectives Incorporated in Treatment for Hepatitis C



## Chronic hepatitis C (HCV) infection is the leading cause of chronic liver disease and liver transplantation in the United States.

Without treatment, up to a third of patients with chronic HCV will develop cirrhosis and complications of end-stage liver disease. Furthermore, HCV-related mortality is on the rise with the aging of baby boomers — the majority of affected individuals.

HCV infection can be resolved by treatment, but the antiviral therapy entails significant side effects that can lead to medication nonadherence and the premature termination of treatment. Until now, few large studies have comprehensively examined patient perspectives about the treatment experience, particularly its social and personal effects.

Patient perspectives can be invaluable to the design and refinement of innovative support strategies in the health care setting. This is illustrated in a recent study of 200 Kaiser Permanente patients after they had received treatment for HCV to understand how their lives were affected. Each study participant was interviewed by telephone, spending about an hour describing their experiences during antiviral therapy and suggesting how the health care system could better support patients during treatment.

Patients ranked physical side effects, psychiatric effects, and employment issues as the most difficult challenges of HCV treatment. Almost all patients reported flu-like symptoms, fatigue, and gastrointestinal problems. Most patients also described depression, and impaired concentration or “brain fog.” Such side effects had an impact on many aspects of the patients’ lives and continued for months after treatment, revealing a need to continue care beyond the treatment course.

The impact of antiviral therapy on employment was significant, and many patients expressed a need for work-related support. Over one-third of working patients suffered severe financial problems, such as job loss, due to treatment. This suggests that health care providers can support patients by facilitating a leave of absence, temporary disability status, or modified work hours during treatment.

The patients also suggested that increased support from treatment providers was needed, such as weekly telephone and/or email check-ins. Patients whose treatment was managed by a nurse or a clinical pharmacist were the most likely to list their treatment provider as someone who supported them through treatment.

The most frequent advice offered for patients receiving HCV treatment in the future was to obtain peer support. Patients reported that friends or family who had previously undergone antiviral therapy were particularly helpful in providing support. Peer support may also offer an antidote to the isolation often experienced during treatment.





## Women's and Children's Health

This section specializes in translational research that bridges the results of epidemiological studies and clinical trials to improve the health of women and children. Kaiser Permanente's electronic medical records provide the ability to link familial records, to examine how health conditions during pregnancy influence the health of offspring, and to link obstetric information with all other aspects of women's health.

We are conducting pioneering research on behavioral and lifestyle interventions to prevent type 2 diabetes in women with gestational diabetes; studying autism to identify genetic and environmental links; researching perinatal health services; identifying biological predictors of diabetes in pregnancy and childhood obesity; understanding how depression and environmental exposures effect perinatal health; and evaluating contraceptive use and clinical data to inform cervical cancer screening practices. The Women's Health Research Institute translates women's health research into clinical practice.

### Primary Research Areas

- Depression and health behaviors before during and after pregnancy
- Lifestyle randomized trials
- Childhood asthma
- Peripartum depression
- Gestational weight gain, diabetes, and hypertension
- Child health services and vaccines
- Environmental exposures and perinatal health outcomes
- Autism spectrum disorders
- Contraceptive use, hysterectomy trends, and cervical cancer



## Telephone Intervention Tested for Women with Gestational Diabetes



**A telephone-based intervention developed by researchers in the Women's and Children's Health section is showing tremendous promise in helping women with gestational diabetes to make lifestyle changes that lower their risk of diabetes type 2 after pregnancy.**

About 8 percent of pregnant women develop gestational diabetes mellitus, typically during the second or third trimester. In addition to delivery complications and health risks to the baby, women with gestational diabetes are seven times more likely to develop type 2 diabetes later on in life.

A team of Division of Research scientists, working in partnership with the Kaiser Permanente Northern California Regional Perinatal Service Center, received \$12 million in funding from the National Institutes of Health and the Agency of Health Care Research and Quality to develop, implement, and evaluate diabetes prevention programs for women with gestational diabetes.

The resulting series of studies demonstrates how translational research — in which the results of successful clinical trials are then rigorously tested in broader populations — can improve care for Kaiser Permanente members and the larger community.

A randomized clinical trial called the Diet, Exercise, and Breastfeeding Intervention tested the feasibility of the phone-based technique with about 200 women with gestational diabetes between October 2005 and June 2009, and showed the intervention's acceptability and effectiveness for weight control.

These encouraging results prompted two randomized lifestyle-intervention trials among larger samples of women in Kaiser Permanente Northern California with gestational diabetes in 2011.

One trial, called APPLES (A Pregnancy and Postpartum Evaluation Program) is testing the phone-based intervention on individuals, while the second trial, called GEM (Gestational diabetes Effects on Moms) is testing it at the health system level by randomizing 44 medical facilities. APPLES works with the women for two years, while GEM is one year long.

Both implemented an integrated program of 13 telephone interviews, diet logs and a fat counter, tip sheets, a website, and a Kaiser Permanente-branded workbook, "Getting in Balance: Diabetes Prevention for New Moms."

Trained dietitians, called lifestyle coaches, utilized a technique that helps motivate patients to make sustainable behavioral changes, helping the mothers to identify barriers, how to overcome them, and how to exercise more and eat less fat.

The DOR team will be analyzing the data this year, and preliminary results appear to show that a large proportion of women were engaged and satisfied with the program.



## Research Program on Genes, Environment, and Health

The Research Program on Genes, Environment, and Health is one of the largest and most comprehensive research resources in the United States, combining data from 200,000 adults to support research on common diseases such as heart disease, cancer, diabetes, Alzheimer's disease, mental health problems, and many others.

The program's goal is to discover the genetic and environmental factors — air and water quality, as well as lifestyles and habits — that are linked to specific diseases and responses to medications, and to apply these findings to improve the health and medical care of Kaiser Permanente members and the society at large.

### 2012 Research Highlights

- ▶ Additional 16,000 participants joined the Research Program to reach a total of 192,000 unique individuals with catalogued biospecimens
- ▶ A total of 81 applications received for use of data and/or biospecimens — 29 applications submitted to funders, 9 successfully funded, 15 under review
- ▶ 16 funded studies in progress in 2012
- ▶ Pregnancy Cohort added biospecimens from 3,770 new participants, bringing cohort total to 8,000 women
- ▶ Database created for integration of genetic, survey, and clinical data
- ▶ Represented at the American Society for Human Genetics Annual Meeting with 10 posters and presentations
- ▶ Results of analyses of Grand Opportunity Project data presented to the director of the National Institutes of Health and other NIH institute directors



# Grand Opportunity Creates Cutting-Edge Research Potential



**In 2009, the Research Program on Genes, Environment and Health (RPGEH) received a Grand Opportunity grant from the National Institutes of Health (NIH) for a project entitled “Developing a Resource for Genetic Epidemiology Research in Adult Health and Aging.”**

When the nearly \$25 million grant was awarded to Kaiser Permanente and the University of California, San Francisco, as part of the American Recovery and Reinvestment Act, President Obama said of the promise this support held: “We can only imagine the new discoveries that will flow from the investments we make today.”

In 2012, RPGEH investigators delivered on all six aims outlined in the original proposal in a day-long symposium with the directors of NIH and the National Institute on Aging. The principal goal of this project has been to create a unique and comprehensive resource that can be broadly used to investigate the genetic and environmental determinants of healthy aging and longevity, as well as aging-related diseases and their treatment.

The project links deep genetic data with information from comprehensive electronic medical records and behavioral and environmental factors on more than 100,000 members of Kaiser Permanente Northern California. In doing so, it creates a powerful platform for ongoing and future research that holds great potential for increasing understanding of the genetic and environmental basis of many diseases and the basis for aging and health as well.

Although there are similar efforts in countries ranging from England to China, this project has unique and special characteristics. The resource includes an extremely rich set of data, including comprehensive, longitudinal electronic medical records; multiyear survey data on relevant behavioral and environmental factors; and newly added genome-wide data and telomere length from 100,000 participants diverse in age, race-ethnicity, and socioeconomic status. A large geographic information system database will capture and map environmental exposures to individual participants, including aspects of the built environment, air quality, and pesticide exposure.

Continuously updating the electronic medical records of cohort members will provide new incident cases and data on the course of disease and response to treatment over many years. The existence of historical data on behavioral and clinical risk factors from prior surveys and clinical records, including multiple measures of alcohol consumption, blood pressure, body mass, glucose tolerance, and lipids, will provide researchers with the opportunity to examine midlife factors in relation to the development of diseases of aging, and to investigate the timing of exposures in relation to disease onset.





## Vaccine Study Center

The Kaiser Permanente Vaccine Study Center helps ensure that the nation's vaccines are safe and effective by conducting research to advance scientific understanding of vaccines in all levels of development. This includes studies evaluating the safety and effectiveness of vaccines both during development and after they have been licensed, and investigating epidemiological factors important to the design and use of new vaccines.

Founded in 1985, the program utilizes Kaiser Permanente's large member population. The Vaccine Study Center conducts clinical trials of new vaccines, which have led to licensing of vaccines to prevent diseases caused by pneumococcus, chickenpox, meningitis, and influenza and other respiratory viruses. The center also partners with government agencies to perform vaccine efficacy and safety studies.

### Primary Research Areas

- ▶ Safety and effectiveness of vaccines before and after licensing
- ▶ Epidemiological factors important to design and use of new vaccines
- ▶ Monitoring of influenza and other respiratory viruses and flu vaccine effectiveness
- ▶ Vaccine safety in special populations
- ▶ Genetic basis of vaccine safety and immune responses

## Study Sparks New CDC Recommendations



**The combination vaccine for measles, mumps, rubella, and chickenpox/ varicella (MMRV) was licensed by the Food and Drug Administration in 2005, and recommended by the Advisory Committee on Immunization Practices (ACIP) in 2006.**

Pre-licensure studies of the combination vaccine among one to two year olds noted higher rates of fever and measles-like rash 1 to 2 weeks after vaccination when compared with separate measles, mumps, rubella (MMR) and varicella (V) vaccines. However, it was unknown at the time of MMRV's licensure whether a higher rate of fevers was similarly associated with an increased risk of febrile seizures (i.e., fever-related convulsion).

In February 2008, Kaiser Permanente researchers alerted the ACIP to preliminary evidence of an increased risk of febrile seizures following MMRV vaccination compared with separate MMR and V vaccines. The Vaccine Study Center subsequently undertook a study in collaboration with from the U.S. Centers for Disease Control and Prevention (CDC) through the Vaccine Safety Datalink project.

Vaccine Study Center researchers used Kaiser Permanente electronic medical records and Vaccine Safety Datalink data from 2000 to 2008 to analyze 459,000 children 12 to 23 months old across the United States receiving their first dose of measles-containing vaccine. This study assessed seizures and fever visits among 12- to 23-month-old children 7 to 10 days following either MMRV or separate MMR and V vaccines.

The study found that although the risk for a febrile seizure after the first dose of MMRV vaccine is low, less than 1 in 1,000, MMRV is associated with a two-fold increased risk of fever and febrile seizures 7 to 10 days after vaccination when compared with same-day administration of separate shots for MMR and varicella vaccines.

Subsequently, the CDC recommended that while either vaccine may be used for the first dose for 1 to 2 year olds, families without a strong preference for MMRV should receive separate MMR and V vaccines. Furthermore, the CDC said that providers who consider using MMRV should discuss the risks and benefits with families and caregivers.

The Vaccine Safety Datalink project is a collaborative effort between CDC's Immunization Safety Office and eight managed care organizations, including Kaiser Permanente's Northern California, Southern California, Colorado, and Northwest regions. The project was established in 1990 to monitor immunization safety and address the gaps in scientific knowledge about rare and serious events following immunization, leveraging robust electronic medical records such as Kaiser Permanente's.





## Comprehensive Clinical Research Unit

One of the opportunities presented to physicians when they join The Permanente Medical Group is the ability to potentially explore their research interests with the assistance of the Comprehensive Clinical Research Unit (CCRU), the consultative arm of the Division of Research that assists clinicians in planning and conducting research within Kaiser Permanente Northern California in conjunction with their local research chair.

The CCRU is a unique entity among Kaiser Permanente regions nationwide, providing research lifecycle support for clinicians and other researchers from project proposal through publication. The CCRU's highly trained, experienced staff offer guidance on research design, project feasibility, budget evaluation, staff planning, project implementation, biostatistical and data analytic services, and collaborative opportunities.

Since launching in 2008 with a staff of three, the CCRU has grown to a staff of 12 at the Oakland regional office and 70 study staff throughout the region, and was reorganized into three subregions to meet demand. As the research support needs of the region increase, the CCRU has strived to meet those needs by expanding services and trainings, developing tools and applications, and raising public awareness of Kaiser Permanente research.

The CCRU has consultative, customer service, operational, and support roles in the region. The Research Collaboration Web Portal developed by CCRU serves as the principal support request system for Kaiser Permanente researchers and staff, non-Kaiser Permanente researchers seeking collaboration with Kaiser Permanente investigators, and potential sponsors to communicate a request to Kaiser Permanente.





In 2012, the program supported over 250 study operational requests from Kaiser Permanente residents, clinicians, and investigators, and provided over 150 formal consultations.

The CCRU has taken research training and migrated it to the Web, offering an on-demand resource through the KP Learn system. The CCRU initially developed two research training courses, Introduction to Clinical Research and Research Statistics, and, at the request of the region, steered the development of an additional statistics course, Regression Modeling, made available in the fourth quarter of 2012. Collectively, the courses provide a strong foundation in clinical research principles, effective clinical research methods, study designs, and basic statistical knowledge.

To streamline and enhance communication and reporting, the CCRU launched the Tracking Research Agreements, Budgets and Contracts system in 2012. The application allows clinical research stakeholders to view their project's status in real-time throughout the lifecycle of the negotiation and execution processes, and serves as a document repository for approved

budgets, and executed agreements and contracts across the different Kaiser Foundation Health and The Permanente Medical Group entities.

In 2010, the CCRU launched KPStudySearch, Kaiser Permanente's first clinical trial and research study search tool ([www.KPStudySearch.kaiser.org](http://www.KPStudySearch.kaiser.org)), which provides detailed descriptions of studies, requirements for participation, and study locations and contacts. In the fourth quarter of 2012, the CCRU began a pilot test of KPStudySearch with the Mid-Atlantic region. KPStudySearch promotes public awareness of research at Kaiser Permanente and has the potential to expand to all regions in 2013.

The CCRU has created a centralized operations infrastructure that supports the needs of clinician investigators, collaborators, and clinical research projects throughout Kaiser Permanente Northern California, and developed a platform to continue growing a quality clinical trials and research program for the region.



## Biostatistics Core

The Biostatistics Core provides expertise to the Division's investigators in study design (including sample size and power calculations), statistical analysis, technical sections in grant proposals, supervision of programmer/analysts in database management and analysis, and manuscript preparation.

Similar support is provided by the Biostatistical Consulting Unit (BSCU) to Kaiser Permanente Northern California physicians and other clinicians who wish to conduct research. With an experienced team of biostatisticians, consultants, programmers, and project managers, the unit provides expertise to clinician investigators. Assistance includes support for biostatistical and programming proposals and projects, feasibility data, data analysis,

result interpretation, and manuscript and presentation preparation. BSCU provides consultations to clinician investigators in developing and executing grants funded by the Kaiser Permanente Community Benefit program and to resident physicians in all phases of their required residency research projects.

Members of the Biostatistics Core also conduct research in statistics that leads to the development of new analytic tools and the improvement of existing ones. This research can improve the quality of the evidence generated by the Division's investigators and the broader research community.



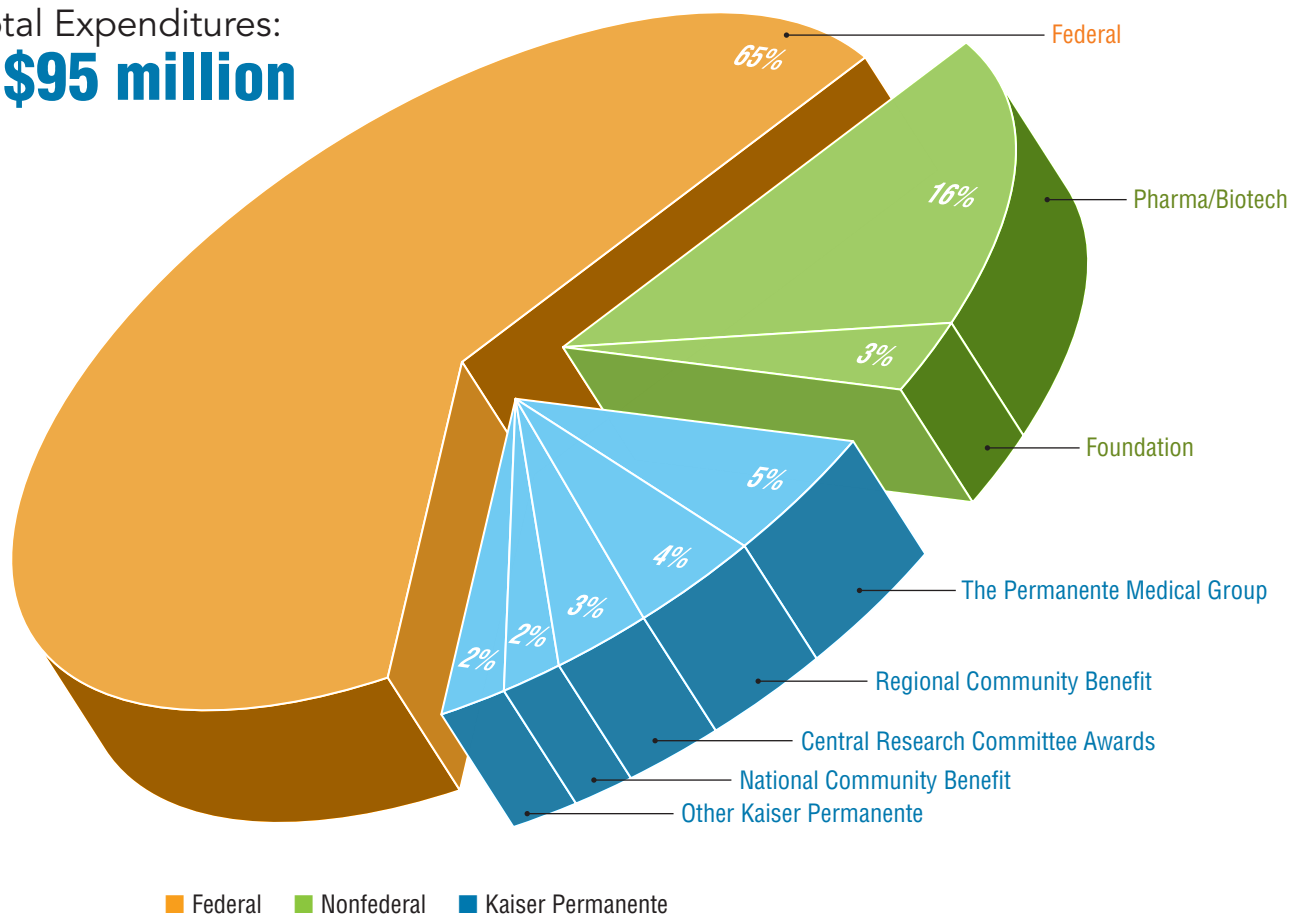
The Division of Research (DOR) is currently home to 62 investigators, with a total of about 550 employees. The DOR also supports 21 adjunct investigators from other academic institutions and has worked with more than 270 clinician collaborators from The Permanente Medical Group. Our scientists are involved in more than 350 research studies. Since its founding in 1962, DOR researchers have published 2,600 scientific papers, including more than 300 papers in 2012.

## 2012 Funding Sources

(Based on expenditures)

Total Expenditures:

**\$95 million**



Kaiser Permanente  
**Research**

**DIVISION OF RESEARCH**  
Northern California

**Scientific and  
Administrative Offices**

2000 Broadway  
Oakland, CA 94612  
510-891-3400

2101 Webster, 20th floor  
Oakland, CA 94612  
510-627-3200

**Research Clinics**

3505 Broadway  
Oakland, CA 94611  
510-891-3400

[www.dor.kaiser.org](http://www.dor.kaiser.org)