

2013 Director's Letter

Partners in research and health

The Division of Research is notable for our distinctive setting within an integrated health care system. All our areas of inquiry — ranging from what causes disease to what interventions lead to better health — involve partnerships with clinicians and patients in the real-life setting of Kaiser Permanente's 236 medical offices and 21 medical centers in Northern California.



In 2013, we brought national attention to the work of Kaiser Permanente through studies that stemmed from our being embedded in a learning health care system. One highlight among many was our paper on the factors that drove the success of a major clinical program to control high blood pressure in patients throughout the region. This study, [published in JAMA](#) last summer, drew plaudits from state and national organizations, and the director of the Centers for Disease Control cited Kaiser Permanente's approach as he urged the entire country to adopt better approaches to hypertension screening and treatment. At the same time, [the chief](#) of our Cardiovascular and Metabolic Conditions Section chaired the national committee that developed comprehensive guidelines for better blood pressure control.

As a progressive and innovative health care organization, we recognize that genetics, environment, and behavior are principal drivers of health and disease. During the last year, we made notable progress in this area through specific investigations into the causes of disease as well as sustained development of our infrastructure for genomic studies. The fact that our portfolio spans the spectrum of basic disease etiology to clinical effectiveness and delivery science creates synergy and enables us to address a full range of opportunities to enhance health.

The Division of Research is also becoming increasingly sophisticated in medical informatics, the field founded by the Division's first director, Morrie Collen. In the 1950s, Dr. Collen and Kaiser Permanente co-founder Sidney Garfield predicted that computers would someday be very useful in the practice of medicine. Today, we are transforming that vision into reality. On the occasion of Dr. Collen's [100th birthday](#) in November, the American College of Medical Informatics convened here for a scientific symposium to honor him and to establish the new medical subspecialty of clinical informatics. We truly have been blessed to have had his guidance for so many years.

The national environment for research funding is tight due to multiple economic pressures, and these are unsettled times for many research groups. We are not immune to these trends, but we are continuing to accomplish high-impact work, and we will maintain our commitment to excellence in research and beneficial influence on the health of our members and communities. We are grateful for the shelter and support of our mature parent organization, which views us as a long-term investment. Our research scientists are extremely talented, they recruit outstanding research teams, and we have strong and capable partners in our administrative, information technology, and strategic programming groups. With our intellectual assets and our integration as part of Kaiser Permanente's learning health care system, I am very optimistic about our future.

Warm regards,

A handwritten signature in black ink that reads "Tracy Lieu". The script is fluid and cursive, with the first name "Tracy" and last name "Lieu" clearly distinguishable.

Tracy A. Lieu, MD, MPH
Director, Division of Research

Above: Tracy A. Lieu, director of the Division of Research, meets regularly with founding director Morris F. Collen.

2013 Collen Centennial



Dr. Morris Collen's medical informatics legacy: "We're in the hope business"

The future of computer-assisted health care can be summed up in one word, Atul Butte, MD, PhD, told a symposium held on the occasion of [Dr. Morris F. Collen's 100th birthday](#).

"Hope."

"We're in the hope business," Butte told some 200 attendees at the symposium and birthday celebration at the St. Regis hotel in San Francisco on Nov. 12, 2013. Attendees included 13 (out of 16) recipients of the [Morris F. Collen, MD, Medal for Outstanding Contributions to the Field of Medical Informatics](#).

Butte, chief of systems medicine at the Stanford University School of Medicine, says that the next 10 years of medical informatics will not just be about algorithms and methods, electronic medical records, genome sequences, open access data and big data, or mobile applications.

"The future of biomedical informatics over the next 10 years is about predicting and preventing the disease before it strikes," said Butte, who was honored by President Obama as a Champion of Change for Open Science in 2013. "It's about explaining those rare diseases that defy experts. It's about keeping people healthy longer, and making sure we apply the right, safe, cost-effective care for patients."

The goals for medical informatics described by Butte could just as easily have been spoken by Dr. Collen in 1961, when he was appointed director of Kaiser Permanente's first medical research department (now the Division of Research) after a 20-year career as a Kaiser Permanente internist. Collen is widely considered the father of medical informatics — a pioneer in the science of using patient data to aid in medical decision-making and to continuously improve health care.

Big data, genomes, and crowdsourcing

Describing himself as "Dr. Collen's academic great-grandchild," Butte shared his predictions for how data and technology will change health care.

In the future, patients will monitor their own vital signs with simple devices and take action to interpret and improve their own health care, Butte said. Apps are already available that allow consumers to "crowd source" health care information — for example, comparing the costs of procedures, medications, and hospital safety scores at different hospitals.

Mapping the first human genome cost \$3 billion dollars and took 13 years, Butte noted. The current cost is \$1,000 for a genome done in a day and a half, and it is predicted to go down to \$33 by 2020.

"We just have to marvel at the innovations we're going to launch, especially in medicine, with these genomes," Butte said. "Genome sequencing is going to drive a lot of medical innovation in the future."

The human genome will be used to predict personal disease risks and prescribe safe and effective mechanisms to prevent them, Butte said, adding that with its Research Program on Genes, Environment, and Health, Kaiser Permanente "is light years ahead of everyone else. We all wish that we could be playing with the data sets that you collect."

The amount of genomic data being made publicly available on the Internet will also continue to increase exponentially in the coming decade, Butte predicted, paving the way for astounding medical discoveries by scientists and citizen-scientists alike.

"Researchers have to share this data on the Internet," Butte said. "Last year, we reached one million gene chips publicly available. In 10 years, we'll have 10 million chips. There are kids downloading this data right now and making discoveries...I think this is going to change the world in 10 years."

Above: Atul Butte (left) of Stanford University described himself as "Dr. Collen's academic great-grandchild"; Morris F. Collen founded the Division of Research in 1961.

More information about [Dr. Collen's 100th birthday](#).

Behavioral Health and Aging

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



Implementation research helps to optimize behavioral health care delivery

A new initiative in 2013 focuses on research that addresses Kaiser Permanente's behavioral health organizational goals — particularly integration, outcomes, and consistency of care — with an emphasis on moving research findings quickly through the operational pipeline into practice.

"Implementation research goes beyond traditional clinical research, which is meant to answer the question, 'What works to improve health for individuals?'" explains [Don Mordecai, MD](#), director of Mental Health and Chemical Dependency Services and Chair of the Chiefs of Psychiatry. "It is about determining what works to allow a large health care system to consistently provide interventions that work to large populations of members.

"Only a few organizations in the country combine a research infrastructure with a large-scale care delivery system. Kaiser Permanente is one, and this initiative is designed to take advantage of this unique partnership."

In 2013, the innovative Behavioral Health Research Initiative (BHRI) was launched in Kaiser Permanente Northern California, supported by the Garfield Memorial Fund and jointly headed by Mordecai and [Connie Weisner, DrPH, LCSW](#), chief of the Behavioral Health and Aging section.

The BHRI team has worked swiftly to establish its foundation in its first year. They have engaged regional and national behavioral health leaders in identifying strategic rapid-cycle research projects in such areas as integration between primary care and behavioral health specialties, access to care, patient outcomes, and transitions in care. Leveraging technology is a common theme in all areas.

Rapid-cycle pilot studies

The team has developed two pilot studies to gather primary data useful for clinical care and for federal grant applications that align with the overall focus of the program, emphasizing strategic projects likely to yield feasible improvements in clinical pathways.

The first study is based on the concept of linkage, in which a continuing-care curriculum links specialty care patients to primary care and integrates their mental health care within the larger health care system. The group-based curriculum is aimed at activating patients to take initiative in managing their health care and helping them link with primary care, complemented by additional specialty services as needed.

Success measures for the Linkage Mental Health pilot study will include patient self-care activation, increased patient satisfaction, and increased patient utilization of Kaiser Permanente's online patient portal.

The program team developed curriculum and protocols for a four-session intervention focusing on depression. The 50-minute sessions involve interactive communication addressing risk and health behaviors, and how to use KP.org and primary care to optimize patient empowerment and better health care.

New model of care for adolescents

A pilot study called Adolescent Behavioral Risk Factor Intervention in Primary Care leverages the promising findings of past projects that examine behavioral health screening, brief intervention, and referral to specialty treatment for adolescents in the Oakland Medical Center Pediatrics Department. The past projects have shown that this protocol increases the identification of risk behaviors and specialty treatment initiation.

The pilot study evaluates the effectiveness of the next step in this new model of care: a group-based Brief Intervention for Behavioral Health, known as the Teen Healthy Lifestyle Groups, for adolescents in a general pediatrics clinic. It involves a series of four sessions that cover a variety of topics, including education on the developing brain, the role and consequences of alcohol and drug use, developing coping skills and building resilience, and interpersonal communication skills, with an emphasis on family communications.

"The foundation has been laid through the work of understanding the mental health and chemical dependency population, and conducting innovative pilot tests," Weisner observes. "Our second year will take further steps in developing work in the larger community, studying technology-enabled interventions, and moving interventions to other regions."

Above: Left to right, Behavioral Health Research Initiative investigators Cynthia Campbell and Enid Hunkler connect with Connie Weisner and Don Mordecai.

Cancer

Investigators in this section study a broad range of cancers, with a major focus on those 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 [Cancer Research Network](#), [Women's Health Initiative](#), and the colorectal cancer component of PROSPR (a national cancer screening study).



Collaborative study seeks to understand early puberty, help prevent breast cancer

A unique collaboration among Division of Research scientists, physicians, and breast cancer advocates is providing critical insights into factors contributing to the early onset of puberty in girls, which has been linked to higher breast cancer risk later in life.

Known as the Cohort study of Young Girls, Nutrition, Environment, and Transitions (CYGNET), the study enrolled about 450 girls between ages 6 and 8 years and has followed them at regular intervals since 2004, allowing researchers to examine a range of influences on puberty benchmarks.

Participants, community contribute to study

The girls in the study are now teenagers, and some have actually become contributors to the study via participation in CYGNET's one-of-a-kind Youth Advisory Board. (The acronym signifies the transition of young girls into mature women — from cygnets to swans.)

"The girls are becoming independent thinkers," says research scientist [Lawrence H. Kushi, ScD](#), CYGNET's principal investigator. "We decided to create a board where our participants are part and parcel of how we do things."

The board meets monthly and the girls have, for example, provided feedback on new study questionnaires and contributed to a brochure describing to their fellow participants what to expect during clinic visits.

The Youth Advisory Board is coordinated by [Zero Breast Cancer](#), a nonprofit organization based in Marin County that has played an integral role in the study since its inception.

Factors influencing earlier puberty

In addition to increased risk of breast cancer, girls with earlier maturation are at risk for a multitude of challenges, including lower self-esteem, higher rates of depression, norm-breaking behaviors, and lower academic achievement. Early maturation also results in greater risks of obesity, hypertension, and several cancers.

"Society is very interested and concerned about earlier onset of puberty," said study partner [Louise C. Greenspan, MD](#), a pediatric endocrinologist at Kaiser Permanente San Francisco. "People want to know what's happening, and they want to know why."

Other new studies in the Cancer section are looking at cancer survivorship and the genetics of skin and lung cancer.

Cancer survivorship

A new \$625,000 study funded by [the National Cancer Institute](#) will examine the role of weight in colon cancer survival.

Led by research scientist [Bette J. Caan, DrPH](#), the study will use computed tomography (CT) scans to assess fat and muscle mass in more than 3,500 colon cancer patients diagnosed between 2005 and 2010 at Kaiser Permanente Northern California. Clinical partners on the study are [Lisa Kinoshita, MD](#), radiologist in Kaiser Permanente's Oakland Medical Center, and [Theodore R. Levin, MD](#), DOR research scientist and Kaiser Permanente gastroenterologist in Walnut Creek.

"This study uses a novel, state-of-the art tool to collect more accurate measures of body composition than standard measures of height and weight, and could provide important insights into the role of energy balance and body composition in cancer survival," Caan says.

Caan is also co-principal investigator on a \$2.2 million study funded by National Cancer Institute (led by [Fred Hutchinson Cancer Research Center](#)). The study will bolster data in the Women's Health Initiative with critical information on cancer outcomes from Medicare and electronic health records, and collect tumor tissue for future studies.

"By enhancing the Women's Health Initiative database with cancer treatment and recurrence data, we will provide valuable resources to examine the effects of cancer diagnosis and treatment on the overall health and quality of life in this cohort," Caan says.

Genetics and skin cancer

Cutaneous squamous cell carcinoma, a skin cancer, is the second most common cancer in America, with over 700,000 cases diagnosed annually; its incidence is on the rise.

A new 4-year, \$1.1 million project led by DOR research scientist [Maryam M. Asgari, MD, MPH](#), will utilize 675,000 bits of genetic information collected by DOR's [Research Program on Genes, Environment and Health](#) to better understand the genetic determinants of squamous cell carcinoma.

"This type of skin cancer tends to run in families," Asgari says. "We seek to improve our understanding and identify mechanisms accounting for its increased inherited susceptibility."

Genetics of COPD and lung cancer

Why do some smokers develop lung cancer, but most do not?

With a new 3-year grant from the California Tobacco-Related Disease Research Program, DOR research scientist [Lori C. Sakoda, MPH, PhD](#), will work toward answering this question.

Sakoda and her research partners are examining the genetic underpinnings of chronic obstructive pulmonary disease (COPD) and lung cancer in former and current smokers, all members of Kaiser Permanente Northern California.

"This study will be one of the most comprehensive examinations of shared genetic risk factors for COPD and lung cancer to date," Sakoda says. "We hope the knowledge gained will contribute toward developing tailored strategies to improve early detection of lung cancer."

Above, (left to right) Shelby Aszklar, Rachael Cornejo, Lawrence H. Kushi, Yesenia Hernandez, and Kristin Soo; the Youth Advisory Board members, who have participated in the CYGNET study since about age 6, collaborate with Dr. Kushi and other researchers on many aspects of the study.

Cardiovascular and Metabolic

Cardiovascular research is a major emphasis at the Division of Research. Studies conducted by the Cardiovascular and Metabolic Conditions section inform 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.



Study closes in on evidence for breastfeeding to reduce future diabetes risk

Gestational diabetes mellitus (GDM) happens in approximately 7 percent of all U.S. pregnancies, and affects over 200,000 women a year. A history of GDM, which refers to glucose intolerance that first occurs during pregnancy, confers up to a seven-fold higher risk of diabetes. Almost 50 percent of women with a GDM pregnancy will be diagnosed with type 2 diabetes within five years after delivery.

Breastfeeding appears to be a first line of defense against a range of adverse metabolic outcomes that can result from GDM. "It is a modifiable health behavior that may play an important role in future disease risk," says [Erica Gunderson, PhD](#), senior research scientist in Cardiovascular and Metabolic Conditions.

Postpartum women with a recent GDM pregnancy who breastfeed have more favorable metabolic profiles, including glucose tolerance, compared with those who do not. However, much less is known about the lasting effects of breastfeeding on development of diabetes later in life.

This is the question that drives Gunderson's Study of Women, Infant Feeding, and Type 2 Diabetes (SWIFT), a postpartum GDM cohort that was created with funding from the National Institutes of Health to determine whether breastfeeding can protect young mothers from developing diabetes after delivery. SWIFT is the first study to prospectively — that is, in real time — examine whether lactation intensity and duration are associated with a lower incidence of type 2 diabetes within two years after a GDM pregnancy, controlling for risk factors influencing breastfeeding success.

Diverse study population

SWIFT study participants include more than 1,000 Asian, Latino, black, and white women of varying socioeconomic status who experienced GDM pregnancies and delivered their infants between 2008 and 2011. The participants were recruited from eight Kaiser Permanente medical centers throughout the 5,000-square-mile Northern California region. The study was highly successful in achieving its enrollment target of 1,035 women within 3 years, and in conducting 2,600 in-person visits to screen this high-risk group for diabetes.

"Our collaborations with KPNC clinicians made the study feasible," Gunderson notes. "It would be unethical to randomize women to breastfeed, so our study design had to ensure that the protective effects are not simply a result of the healthier lifestyles for women who chose to breastfeed."

Follow-up of the SWIFT cohort is currently underway to evaluate both short- and long-term effects of breastfeeding intensity and duration on maternal glucose homeostasis and incidence of type 2 diabetes during the follow-up period.

"If lactation is found to have persistent effects on maternal glucose metabolism that prevent type 2 diabetes in women, then translation of these findings may have a significant public health impact," she says. "Lactation promotion would be a low-cost, feasible strategy that may enhance postpartum behavioral interventions for the prevention of diabetes and other metabolic conditions in women."

Impacts on care delivery

Gunderson's findings are already influencing care delivery efforts. Jocelyn Audelo, senior consultant at the Kaiser Permanente Care Management Institute and coordinator of a national Healthy Beginnings Community of Practice, says: "Erica has been exceptionally proactive — lending expertise to our Healthy Beginnings leads and front line staff, interpreting the literature, and sharing her research with us."

"Her findings on the risk factors for unsuccessful lactation in women with GDM, for example, have greatly influenced our planning for targeted support to enable women with GDM to experience the benefits of lactation for their own future health and that of their infants."

Above: Research shows that breastfeeding may be a first line of defense against adverse metabolic outcomes that can result from gestational diabetes mellitus.

Genomic Research



Genomic research reaches milestones and raises questions

The [Research Program on Genes, Environment, and Health \(RPGEH\)](#) reached another major milestone in 2013 — the single largest deposit of data into dbGaP, the database of Genotypes and Phenotypes, housed in the [National Center for Biotechnology Information](#) at the National Institutes of Health (NIH).

The data come from 78,482 ethnically diverse participants in the research program whose DNA was genotyped as part of the RPGEH Grand Opportunity project, and who consented to have their de-identified data placed into dbGaP. The data set contains over 650,000 genetic markers, or genotypes, and includes indicators for 22 diseases and medical conditions. NIH will provide access to the data for scientists from all over the United States and around the world who apply to use it for research on health.

"The transfer of these data will greatly accelerate research on the genetic and environmental influences on health, disease, and aging," notes [Catherine Schaefer, PhD](#), executive director of RPGEH. "By making this deep genomic data on such a large diverse cohort broadly available, we are enabling many more scientists to work at a much greater scale that is likely to help answer important questions concerning health."

"It's all about time and money," adds [Neil Risch, PhD](#), RPGEH co-director and director of the Institute for Human Genetics at University of California, San Francisco (UCSF). "Collecting large amounts of health data from people — and processing it — is labor intensive and expensive. With this data set, no one has to take bio samples, safeguard and store them, or conduct a genome-wide analysis of their DNA. They can simply sit at a computer, ask questions of the data, and extract information."

This resource gives researchers an entirely new platform for studying genetic and environmental influences over time on a wide variety of health conditions, across diverse populations. It represents, say Schaefer and Risch, "a radical shift in genomic and epidemiological research."

Translational genomics center launched

This year also saw the establishment of the new Center for Transdisciplinary ELSI Research in Translational Genomics — called CT2G — a joint project of Kaiser Permanente, UCSF, and UC Hastings College of Law. The three-year program will explore the ethical, legal, and social implications (ELSI) of genomics in health care.

"In the future, there is the belief that everyone will have their genome sequenced, and that information will be used to guide medical care," says Carol Somkin, PhD, research scientist with the Kaiser Permanente Division of Research. "Yet many questions remain about how best to use this information so that it improves outcomes and maintains patient trust."

"A decade after the human genome was fully mapped, figuring out how to translate genomic findings into prevention and clinical care has become a public health priority," adds Barbara Koenig, PhD, professor of medical anthropology and bioethics in the UCSF School of Nursing.

Somkin and Koenig are co-directors of the new center, which will foster cooperation among a broad range of stakeholders, including scholars, scientists, policymakers and clinicians from multiple fields and specialties. The multidisciplinary effort seeks to begin to answer the thorny questions about how genomic information will be used — before this scientific revolution enters the clinical realm.

"These new genomic discoveries raise complex ethical and social issues," says Julie Harris-Wai, PhD, MPH, staff scientist at the Kaiser Permanente Division of Research and associate director of the new center. "We have to be able to work across many disciplines to get something that's useful to individuals. We will identify target areas and work collectively to come up with guidelines and advice for translating genomics information into clinical care."

Above: Left to right, Catherine Schaefer, Sarah Rowell, and Eric Jorgenson visit the Kaiser Permanente Biorepository.

Health Care Delivery and Policy

Investigators in the Health Care Delivery and Policy 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.



Studies explore innovative uses of technology to improve patient outcomes

A growing portfolio of DOR studies focuses on new uses of technology to facilitate communication between doctors and patients, with the goal of improving health for patients with chronic and difficult-to-manage conditions. The Division is also taking a leading role in the development of a new national network of health care data for patient-centered outcomes research.

Symptom tracker for diabetes patients

Research scientist [Alyce S. Adams, PhD](#), has launched a study aimed at improving the quality of life for patients suffering from diabetic peripheral neuropathy (DPN), which affects an estimated 5.5 million people — about half of patients with diabetes. Symptoms of DPN may include pain, tingling, burning, and numbness that start in the feet. In addition to problems such as sleep loss and limited mobility, DPN can ultimately lead to foot amputation if not addressed.

Medications are available to treat DPN, but may require frequent changes to achieve symptom relief, and they typically don't eliminate all symptoms; some patients may stop taking them due to unpleasant side effects.

"Treatments may need to be tailored to meet the needs of each patient," says [Marc G. Jaffe, MD](#), endocrinologist at Kaiser Permanente's South San Francisco Medical Center and a clinical collaborator on the DPN study. "It takes a strong commitment on both sides."

Patients recruited for the study will receive three interactive voice response calls asking them to evaluate their DPN symptoms over a 6-month period. Their responses will be fed back to their doctors. Outcomes will be measured in terms of changes in patient quality of life, as well as in changes in prescribing and medication-taking behavior in response to patient reports.

The \$1.9 million study is funded by the Patient-Centered Outcomes Research Institute (PCORI), a federal agency founded in 2010 as part of the Affordable Care Act to promote evidence-based research that helps patients and providers make more informed decisions.

Pre-visit prioritization for office visits

Patients with multiple chronic conditions are the focus of a new study led by research scientist [Richard W. Grant, MD, MPH](#). Due to the aging of the population and advances in health care, by 2020 an estimated 130 million Americans will have one or more chronic conditions.

This five-year study targets patients with type 2 diabetes, who are often managing other medical conditions such as heart disease, obesity, arthritis, and depression. In addition, complex patients with chronic conditions often also deal with non-medical issues such as financial barriers or other life stresses.

With \$2.9 million in funding from the National Institute of Diabetes and Digestive and Kidney Disorders, Grant is developing an online tool that will guide patients through a prioritization process prior to office visits.

"Sometimes the most urgent things are those that get addressed first. If it's not as urgent or not perceived as urgent it might not get addressed at all," says [Eileen Kim, MD](#), primary care diabetes clinical leader for Kaiser Permanente Northern California and a clinical collaborator on the study.

"The goal is to avoid the common situation where the doctor is on his or her way out of the room after the visit, and the patient says 'Oh, by the way...'," Grant says. "Our hypothesis is that we can have better diabetes control if the patient and doctor are both on the same page."

National network for patient-centered research

A \$7 million PCORI funding award will take advantage of Kaiser Permanente's pioneering expertise in health care research to develop a network of data systems for conducting patient-centered outcomes research for a variety of health conditions, starting with colorectal cancer, congenital heart disease, and obesity.

Called the Patient Outcomes Research To Advance Learning (PORTAL) Network, this project brings together four leading health-care delivery systems (Kaiser Permanente, Group Health Cooperative, HealthPartners, and Denver Health); the 10 research centers affiliated with these systems; and their patients, clinicians, and operational leaders. The group will lay the foundation and develop new approaches that use the health care systems' powerful electronic medical records, and engage patients and other stakeholders to design research on important health problems, including both common and rare diseases.

The PORTAL Network is led by principal investigator [Elizabeth McGlynn, PhD](#), director of Kaiser Permanente's Center for Effectiveness and Safety Research, and co-principal investigator [Tracy A. Lieu, MD, MPH](#), DOR director.

"This grant presents a terrific opportunity to further develop Kaiser Permanente's vision of using computerized data to help patients achieve better health," Lieu says. "This vision was first described more than 50 years ago by [Morrie Collen](#), the founding director of our research program. We have world-class leaders in research in the three focus areas for our network, colorectal cancer, congenital heart disease, and obesity. This is a great chance for us to transform health care through patient engagement."

Above: Mark Jaffe (left) and Alyce Adams are working on a study to improve treatment of diabetic peripheral neuropathy.

Infectious Diseases

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



HIV treatment moves from tending to the dying to caring for the aging

In 1995, the Food and Drug Administration approved the first protease inhibitor and ushered in a new era of highly active antiretroviral therapy. It was shortly after this critical turning point in the history of HIV that [Michael Silverberg, PhD, MPH](#), joined the Division of Research. It was an opportunity that he says was created at the request of HIV clinicians in Kaiser Permanente Northern California who desired a research partner to study the emerging clinical issues among patients with HIV.

"The theme of my research has mirrored the changes in demographics of the HIV population," Silverberg says. "As our HIV population ages, research has shifted to investigating their unique medical issues, such as contending with the increased burden of multiple age-related illnesses or conditions."

He does not have to search far for inspiration; he meets quarterly with HIV clinicians from the Kaiser Permanente Northern California region, who bring ideas for research to him.

"Now that people with HIV — even those who contracted it in their twenties — are growing older, we need to monitor and manage the conditions that come with aging," he notes. "These are the same conditions as the general population — cancer, cardiovascular disease, dyslipidemia, liver disease — but with the added burden of long-term immunodeficiency. HIV patients themselves also tend to have a higher prevalence of other risk factors."

Heart attack risk study

For example, HIV-positive individuals are known to have higher risk of heart attacks because they are more likely to smoke and to smoke heavily compared to the general population. In addition, HIV infection may directly increase plaque formation, and some HIV therapies may increase cholesterol levels, which in turn increases the likelihood of a heart attack. "We have to help our HIV population manage their risk factors for heart attacks and other diseases because there is less room for error," Silverberg explains.

This past year, Silverberg collaborated on a study of heart attack risk with [Daniel Klein, MD](#), chief of infectious diseases for Kaiser Permanente Hayward-Fremont, who has treated HIV-infected individuals for more than 25 years and was among the first to describe the association between HIV and heart disease. Their investigation sought to clarify the extent to which HIV-associated immunodeficiency was associated with the risk of a heart attack.

The results, [published in the *Journal of Acquired Immune Deficiency Syndromes*](#), determined that HIV-positive individuals with lowest-recorded CD4 cell counts of 500 or more had no greater risk of a heart attack than HIV-negative subjects. A CD4 cell count below 500 cells per microliter is considered a sign of a weakened immune system.

"It is biologically plausible that lowest recorded CD4 cell count acts as a risk factor for heart attack since atherosclerosis is considered a consequence of a chronic inflammation," notes Klein. "The strong association for lowest recorded CD4 cell count and myocardial infarction risk likely reflects the fact that it is a good surrogate for increased duration of immunosuppression and HIV-associated inflammation."

This growing body of research is influencing new treatment guidelines that increasingly emphasize preventive medicine for HIV patients who are living longer.

"The epicenter of the AIDS epidemic was Northern California," Silverberg reflects. "So we are seeing the onset of conditions of aging first. This affords us an opportunity to be in the forefront of research and treatment for the aging HIV population."

Above: A growing body of research is influencing new treatment guidelines that increasingly emphasize preventive medicine for HIV patients who are living longer.

Women's and Children's Health

The Women's and Children's Health section specializes in translational research that improves the health of women and children. We are conducting pioneering research on type 2 diabetes prevention in women with gestational diabetes; studying autism; researching perinatal health services; identifying causes of childhood obesity; and evaluating cervical cancer screening practices.



Big data, pregnancy studies aim to improve health care for babies

Robust neonatal data sets at the Division of Research are helping to ease the way for Kaiser Permanente's smallest members.

"Every year, we provide care for 35,000 newborns and 350 very-low-birth-weight infants under 1,500 grams," says [Allen Fischer, MD](#), regional director of neonatology for Kaiser Permanente Northern California.

Since 1993, DOR has been collecting demographic and clinical data on every infant born in the region, which currently amounts to more than 800,000 records. In addition, another data set aggregates data on infants admitted to neonatal intensive care units (NICU) — currently over 50,000 records.

"No single hospital could possibly do that," Fischer says. "The staff and resources at DOR to collect, collate, report, and analyze data and put it in a presentable format — so that the clinicians can plan their quality activities — is indispensable."

Systemwide health care improvements for newborns and preterm infants made possible in recent years by the neonatal data sets include:

- The development of an online calculator to help doctors predict the risk of sepsis in newborns, and treat or monitor them appropriately.
- The identification of effective strategies to reduce dangerous bowel infections in preterm infants (called necrotizing enterocolitis).
- Reductions in the number of days infants spend in the NICU.
- Fewer blood-stream infections associated with central intravenous lines.
- Greater percentages of high-risk infants born at Kaiser facilities with high-level NICUs, eliminating the need for infant transport.

"Neonatologists may be considering changes in practice. We can look at the data to inform their decisions," says research scientist [Michael Kuzniewicz, MD, MPH](#), who manages the neonatal data sets.

Autism and preterm infants

The neonatal data sets have also yielded important insights on the role of gestational age at birth in subsequent diagnoses of autism spectrum disorders.

Researchers analyzed records on more than 195,000 infants born at Kaiser Permanente hospitals between 2000 and 2007, and identified autism diagnoses made through Jan. 31, 2011, in children 3 years or older.

In a study published in October 2013 in the [Journal of Pediatrics](#), Kuzniewicz and colleagues reported that 1.78 percent of preterm infants born at under 37 weeks were subsequently diagnosed with autism, as compared to 1.22 percent of those born at 37 weeks of gestational age or older. In general, autism spectrum disorders were about three times more common in infants born at 27 weeks or less compared with infants born at term.

"We found that each additional week of prematurity increased the risk of an autism spectrum disorder," says [Lisa A. Croen, PhD](#), the study's senior author and director of DOR's [Autism Research Program](#). "Additional studies will be needed to help us understand the biological mechanisms underlying these findings."

Managing gestational weight gain

Two new clinical studies are examining pregnancy-related factors to ensure healthy outcomes for mothers and their babies.

A new \$3.8 million, 5-year study funded by [National Institute of Child Health and Human Development](#) is investigating a diet and lifestyle intervention to help overweight and obese women gain the appropriate amount of weight during pregnancy.

"Preventing excessive gestational weight gain in overweight and obese women has the potential to reduce women's risk of obesity, as well as the risk of obesity in their children," says [Assiamira Ferrara, MD, PhD](#).

Women will be enrolled in the intervention at 10 weeks of pregnancy. They will receive two in-person counseling sessions and 11 telephone sessions with trained dietitians, with the goal of having them gain weight at appropriate levels, as recommended by the Institute of Medicine.

"This intervention will be evaluated for possible translation and adoption by the entire Kaiser Permanente Northern California system," notes Yvonne Crites, MD, a clinical partner on the study and medical director of the KPNC Regional Perinatal Service Center.

Depression and pregnancy

An estimated 15 to and 20 percent of women suffer from depression during pregnancy, increasing the risk of adverse pregnancy outcomes including preterm delivery and low-birth-weight babies.

"These are the leading causes for infant mortality and morbidity, resulting in significant burdens to families and society," says research scientist De-Kun Li, MD, PhD, MPH.

Li is collaborating with Tracy Flanagan, MD, director of women's health for Kaiser Permanente Northern California, on a new \$2.1 million study to identify the best treatments options for depression during pregnancy.

Funded by Patient Centered Outcomes Research Institute, the study will take advantage of KPNC's newly implemented universal peripartum-depression screening program to compare pharmacotherapy, psychotherapy, and combination treatments, as well as no treatment at all.

"The findings will provide answers to long-standing patient and clinician questions of whether depression in pregnancy should be treated, and which options are most effective in improving fetal outcomes," Li says.

Above: Quality improvements have included fewer hospital-acquired infections, fewer days spent in the NICU, and better sepsis treatment for babies.

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.



Pertussis outbreak aids understanding of vaccine effectiveness

The pertussis outbreak of 2010 and 2011 in California offered a rare window through which to examine the long-term effectiveness of a whole cell vaccine versus an acellular version, and witness how the protection that a vaccine affords can decline over time. A study by the co-directors of the Vaccine Study Center seized the opportunity to gain greater understanding of how a vaccine's effectiveness wanes.

Pertussis, or whooping cough, seemed to have mostly disappeared from the United States by the late 1970s, but over the past 20 years the disease has bounced back. Despite high levels of vaccine coverage, pertussis epidemics have arisen every 3 to 5 years since the 1980s, with progressively higher incidence rates over time. Most recently, California had the largest pertussis outbreak in 50 years during 2010-2011. Researchers have suspected that the replacement of the whole-cell pertussis vaccine with an acellular vaccine may be the reason why.

Whole-cell pertussis vaccines (DTwP) were available from the 1940s to 1990s, but were associated with safety concerns that ultimately led to the development of acellular pertussis vaccines (DTaP). By the late 1990s, the United States had switched from whole-cell to acellular vaccines for all five recommended infant and childhood doses.

A study by Vaccine Study Center co-directors Nicola Klein, MD, PhD, and Roger Baxter, MD, published in *Pediatrics*, examined 10- to 17-year-olds who received the recommended pertussis vaccines and evaluated the risk of pertussis during the 2010-2011 outbreak according to the number and type of pertussis vaccines (whole-cell and/or acellular) they had received as infants and toddlers. The findings confirmed that the whole-cell vaccines were more effective at protecting against pertussis than the acellular vaccines.

"Studies have suggested that protection following the acellular pertussis vaccine is less enduring than following the whole-cell pertussis vaccine," Klein says. "Although reasons for the recurrent pertussis outbreaks are complex, waning protection following five doses of acellular pertussis vaccine plays a central role, at least in recent epidemics."

Acellular versus whole-cell vaccines

Teenagers who were vaccinated with four doses of acellular vaccines were at almost six times higher risk of pertussis than were those who had received four doses of whole-cell vaccines. Persons who received mixed whole-cell and acellular vaccines had an intermediate level of risk between those who received all whole-cell or all acellular vaccines. Those who received mixed vaccines were at nearly four times higher risk of pertussis than were those who received all whole-cell vaccines.

Increased number of acellular doses from zero to four was significantly associated with an increasing percentage of positive pertussis tests. On average, individuals had a 40 percent increased risk of pertussis for each additional acellular dose received (as compared to receipt of a DTaP dose) between ages 1 and 24 months.

Earlier studies by the Vaccine Study Center have shown that protection from the fifth dose of acellular pertussis vaccine wanes substantially during the 5 years after vaccination among children 4 to 12 years of age who have received only the acellular vaccine. The current study included only individuals born in 1999 or earlier, for whom at least 5 years had passed since receipt of the fifth pertussis vaccine.

The results of this and other studies, the researchers note, highlight the need for new pertussis vaccines that provide both an improved safety profile and long lasting immunity. "The findings of waning immunity associated with ongoing outbreaks of pertussis clearly are a call for the development of more effective and durable pertussis vaccines."

However, Baxter and Klein emphasize, the DTaP vaccine is effective and remains an important tool for protection against whooping cough for children and the communities in which they live, and following current CDC recommendations remains important.

Above: While pertussis vaccines could be improved, following current CDC recommendations for infant and child immunization remains the best protection parents can give their children.

Virtual Research Office



Virtual Research Office provides study tools for doctors

Kaiser Permanente Northern California doctors who do research — or want to do research — now have a new tool for getting the support that they need.

"One of the biggest challenges that we have had is that we have a lot of different resources but no single, integrated way to get them to the doctors when they need it and how they need it," says Alan S. Go, MD, director of the Comprehensive Clinical Research Unit and regional medical director of clinical trials.

"The [Virtual Research Office](#) is a one-stop shop — a jumping off place for what doctors interested in doing research want to do," Go says. "We're the right starting point for almost everybody considering a research study. In addition, we can connect doctors to Kaiser Permanente researchers who are working in the same areas so they may not have to start from scratch."

The Virtual Research Office brings together resources for:

- Study planning, including feasibility assessment, budgeting, and grant writing
- Research methods and other training, legal, and human-studies requirements
- Recruiting and data management tools for clinical trials and research studies
- Data analysis, biostatistics, and programming support referrals

Plan before recruiting

Go urged busy clinician researchers to contact the Division of Research before they start planning their studies, in order to avoid common research pitfalls.

For example, he cited the case of a Kaiser Permanente emergency medicine doctor who was trying to identify patients with chest pain who could safely be discharged from the emergency department. "He had collected data and didn't know what to do with it," Go says. "The study wasn't designed correctly, and after four years he could draw no conclusions. That was really unfortunate. If we had started with him from the very beginning of planning the study, we would have had a much better outcome."

Susan Campbell, manager of the clinical trials unit for Kaiser Permanente San Francisco, interacts regularly with the Division of Research on a variety of studies, including ones involving treatments for HIV, heart disease, rheumatoid arthritis, and hepatitis.

While Campbell's well-staffed unit manages 30 to 40 clinical trials at one time, doctors based at other Kaiser Permanente medical centers "may not have anyone to go to for assistance," she says. "Certainly they need access to a friendly and easy-to-use website where they can easily go and see, for example, what training and resources they need."

The website is a conduit for connecting with the Division's Comprehensive Clinical Research Unit, Biostatistical Consulting Unit, the regional Institutional Review Board, and more.

"We hope that researchers both outside and inside the Division of Research will use the Virtual Research Office," Go says. "If you have specific questions that you need answered, contact us first. The result can be a better project all around."

Above: DOR's new Virtual Research Office will help doctors get assistance with planning and carrying out studies, and analyzing data.

Fellows and Scholars



MD fellows pursue delivery science research

In 2013, the Division of Research announced its new [Delivery Science Fellowship](#) program, with the goal of training the next generation to translate research findings into clinical care.

Led by DOR research scientists [Richard W. Grant, MD, MPH](#) (director), and [Julie Schmittiel, PhD](#) (associate director), the 2-year, full-time program includes mentorship on delivery science projects, career and skill development seminars, the opportunity for concurrent academic study with the UC Berkeley School of Public Health, and an optional part-time clinical appointment.

The first class begin their fellowships in July 2014:

Mark Lin, MD, is completing his Family and Community Medicine Fellowship at San Francisco General Hospital. He will be mentored by [Alyce S. Adams, PhD](#); his interests include primary care redesign and patient-centered outcomes research.

Lin was drawn to the DOR fellowship program's unique set of strengths: "As a resident physician who has long admired the research produced by Kaiser Permanente, I am honored to have the opportunity to work alongside some of the top researchers in the country who are passionate about improving the delivery of health care."

Lin's career goals have always included improving public health as well as providing primary care as a family medicine physician. "This fellowship will allow me to do just that by complementing my medical education with the skills necessary to research innovative ways to improve the delivery of health care in my community."

Yan Kim, MD, completed her UCLA Pulmonary Critical Care Fellowship in 2012 and is currently completing PhD work. Her interests are focused on end-of-life care and advanced directives, and she will be mentored by **Gabriel J. Escobar, MD**.

Kim said the fellowship will provide hands-on experience from seasoned research scientists on essential skills such as grantsmanship, manuscript publication, and effective presentations, helping her to pursue the goal of becoming an independent research scientist.

"Kaiser Permanente offers the ideal setting for delivery science due to its integrated care model, comprehensive electronic health record, and commitment to providing high-quality patient care," Kim says.

DOR supports public health scholars

The Kaiser Permanente Public Health Scholars Program is now in its 5th year of collaboration with the East Bay Community Foundation and the School of Public Health at the University of California, Berkeley. The program is designed to meet the increasing need for diverse public health workers by providing students the opportunity to receive their education at one of the nation's premier schools of public health. To date, Kaiser Permanente has been able to support 83 students with scholarships.

"Kaiser Permanente recognizes the importance of a vital public health system," says **Raymond Baxter, PhD**, senior vice president of Community Benefit, Research and Health Policy. "Our nation is experiencing an unprecedented demand for highly trained and dedicated public health workers. We established this scholarship fund to enable students to pursue their studies in this field and deliver their expertise to vulnerable communities."

Two of the 16 Kaiser Permanente Public Health Scholars selected in 2013 are augmenting their studies with work and training at the Division of Research.

Vicky Gomez, now a 1st-year doctoral student, received her MPH in community health education from San Francisco State University in 2009. Born and raised in San Francisco's Mission District, she began working at Kaiser Permanente in 2006. As research associate in the Division's Cancer Section, she works with **Carol Somkin, PhD**, in cancer prevention and behavioral studies.

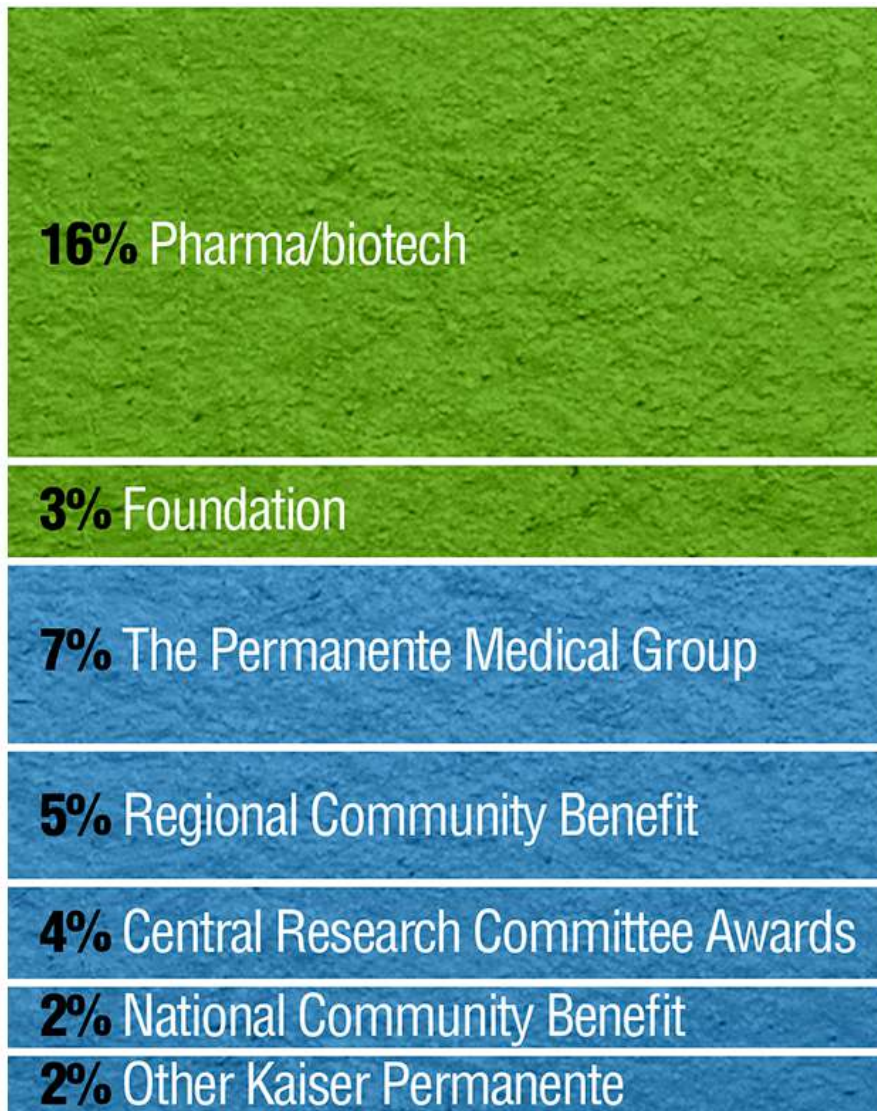
She was recently awarded a diversity supplement from the National Cancer Institute to conduct a colorectal cancer screening pilot study in the faith-based Latino community of Alameda County. The project will inform her dissertation for her DrPH degree and feed her passion to eliminate cancer health disparities in the Latino community by developing culturally sensitive interventions that reduce barriers to screening and health care access.

Felisa Gonzales is a postdoctoral fellow with the Cancer Prevention Fellowship Program at the National Cancer Institute. Currently, she is pursuing a master of public health in epidemiology and working at the Division with [Lawrence H. Kushi, ScD](#), on analyses in the CYGNET study, which examines environmental and genetic factors in the development of early puberty. Her interest in public health was sparked during her studies in Guatemala, where she had spent time volunteering at a local pharmacy and was struck by how issues of access and poverty can influence someone's health. When she returned home and had the opportunity to work on behavioral health studies, she realized, "I didn't really have to travel all the way to Guatemala just to experience health disparities — they are occurring here in my own Latino community."

Above: Left to right, Mark Lin, Yan Kim, Vicky Gomez, Felisa Gonzales.

More info on [Delivery Science Fellowships](#).





The Division of Research (DOR) is currently home to 60 investigators and staff scientists, with more than 550 employees. The DOR also supports 21 adjunct investigators from within Kaiser Permanente and 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 1961, DOR researchers have published 2,900 scientific papers, including more than 300 papers in 2013.