2016 Director’s Letter

Understanding Health and Transforming Health Care: Synergy in Research

The idea that research is integral to a learning health care system has become au courant, but it’s far from revolutionary. Two of Kaiser Permanente’s founders, Sidney Garfield and Morrie Collen, considered research, clinical care, and teaching the three pillars of a great health care organization. Today, Kaiser Permanente is internationally respected for research that transforms health by discovering the key drivers of health and disease, and identifying effective and efficient ways to deliver health care.

In 2016, the Division of Research continued to build on the synergy between two interlocking objectives in our research mission: understanding health and transforming health care. Let me offer three examples.

In cancer, our epidemiologists continued groundbreaking work in areas such as nutritional and social factors that influence survival after a breast cancer diagnosis. The decades of work our researchers have done to understand and develop our clinical data have been paying off in the clinical realm, with our research contributing a key element toward the commendations our Kaiser Permanente Northern California medical centers have earned en route to being accredited as cancer centers of excellence.

In cardiovascular disease, the landmark CARDIA study celebrated its 30th year of patient follow-up. (Above, third from left, Bernard J. Tyson, Chairman and CEO of Kaiser Foundation Health Plan, Inc. and Hospitals; left, CARDIA principal investigator Stephen Sidney, MD, and study participants.) The diverse patients recruited by our team here in Northern California have enabled us to identify early-life risk factors for later cardiovascular disease. Our cardiovascular research portfolio extends to key clinical issues such as reducing disparities in hypertension and accurately predicting a patient’s risk of heart attack or stroke.
In behavioral health, we completed an innovative, NIH-sponsored study to engage patients receiving addiction treatment by using health information technology resources available in Kaiser Permanente’s electronic health record. This study’s successful approach is now being implemented regionwide, and is viewed as a model for intervention in related fields.

We have many more examples of synergy between epidemiology and health care delivery research in areas including women’s and children’s health, diabetes, and infectious diseases. I’m proud of our researchers’ success in obtaining external funding from the NIH and other important sponsors. At the same time, over the last few years, we have increased our internally funded work, enabling us to address key operational areas such as predictive analytics, which uses data to establish the best approaches to current medical problems and identify opportunities to intervene and avoid problems in the future. We also have increased our collaborations with physicians of The Permanente Medical Group via exciting new programs in delivery science – research that involves evaluating clinical or organizational practices that health care systems can implement or encourage.

Looking forward, our strengths in scientific talent, our natural resources in terms of rich data, and our relationships in a learning health care system ensure our ability to produce high-impact research. We have built synergy among the varied components of our research portfolio, and our diversity of skills and interests enriches our collective scientific imagination as well as our robustness as a research group.

Warm regards,

Tracy Lieu, MD, MPH
Director, Division of Research
2016 Research Highlights

Behavioral Health and Aging

**Landmark report on alcohol, drugs and health:** Facing Addiction in America: The Surgeon General's Report on Alcohol, Drug and Health marks the first time a U.S. Surgeon General has dedicated a report to substance misuse and related disorders. The report addresses neurobiology, prevention, treatment, recovery and health systems integration. Constance Waisner, DrPH, senior research scientist, wrote the report’s chapter on health care systems. Read more

**Ethnic disparities in brain health:** A new 5-year, $13 million study will revisit physical exams undertaken from the 1960s through the 1980s to evaluate how risk factors in early and mid-life have affected brain health and dementia risk among a large, ethnically diverse cohort of seniors. Principal investigator Rachel Whitmer, PhD, will partner with the University of California, Davis, Alzheimer’s Disease Center to undertake state-of-the-art brain imaging and cognitive testing of study participants, with funding from the National Institute on Aging. Read more

**Empowering addiction treatment patients:** In the first trial of an intervention focused on increasing alcohol and drug treatment patients’ engagement in their health care, researchers found that the patients who received the full course of intervention sessions had greater involvement in managing their health, as well as higher abstinence rates and longer treatment retention. As reported in *JAMA Psychiatry*, the intervention is innovative in its use of electronic health records and patient portals to engage patients and facilitate communication with their medical providers. Read more

**Dementia risk among racial/ethnic groups:** In the first and largest study to look at a population representing the diversity of the United States, researchers compared six ethnic and racial groups within the same geographic population and found significant variation in dementia incidence among them. Researchers found dementia incidence to be highest in blacks and American Indian/Alaska Natives, lowest among Asian Americans, and intermediate among Latinos, Pacific Islanders and whites. Read more

**Kaiser Permanente Research Biobank:** Recruitment was officially launched in April for the Kaiser Permanente Research Bank, a long-term research resource designed to help the researchers better understand how people's health is affected by their genes, behaviors and the environment. The goal is 500,000 participants who represent membership in all Kaiser Permanente regions, which would make it one of the world’s largest and most diverse repositories of genetic, environmental and health data. Cathy Schaefer, PhD, leads the research bank effort in Northern California. Read more
Biostatistics

Research consultations: Under the direction of Mary Anne Armstrong, MA, in 2016 the Biostatistical Consulting Unit provided support for 152 resident and fellow research projects, 20 miscellaneous funded projects, and 10 miscellaneous unfunded consultations (via funding from the Comprehensive Clinical Research Unit); and helped clinical partners develop 39 Community Benefit grant proposals. The unit also provided intensive consultations on 24 Community Benefit projects that were funded in 2016. Throughout the year, unit staff contributed to 17 publications and 37 conference presentations for their clients.
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Causal inference software: Recent decades have seen considerable advances in the development of formal causal-inference methodologies and in the development of statistical methods for the rigorous evaluation of the effect of a sequence of clinical decisions using electronic health record data. In collaboration with academic partners, DOR researchers, led by Romain S. Neugebauer, PhD, have developed software to facilitate the more routine application of these statistical methods. Several R and SAS products have been released in 2016 for applications in on-going and future studies.
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Preserving privacy in patient-centered research: A new study funded by the Patient-Centered Outcomes Research Institute, with co-investigator Bruce Fireman, MA, will develop privacy-protecting analytic tools for PCORI networks to perform rigorous analyses without sharing potentially identifiable patient-level information. Researchers will assess benefits of, and barriers to, implementing these analytic tools in multi-site PCORI studies.
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Cancer

Fecal immunochemical screening tests: When used in a large health care system, the fecal immunochemical test (FIT) was sensitive for detecting colorectal cancer and adherence to recommended annual follow-up testing was high, according to a study by Douglas A. Corley, MD, PhD, and colleagues, published in *Annals of Internal Medicine*. The analysis of 323,000 members at Kaiser Permanente Northern California who chose FIT for colorectal cancer screening found that the vast majority (over 80 percent) were willing to continue taking the test year after year, as recommended.

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Vitamin D and breast cancer mortality: Women with higher vitamin D levels in their blood following a breast cancer diagnosis had significantly better long-term outcomes; according to a study by Lawrence H. Kushi, ScD, and colleagues published in *JAMA Oncology*. Based on data from the Pathways study of breast cancer survivorship, the study found that women with the highest levels of vitamin D had about a 30 percent better likelihood of survival than women with the lowest levels of vitamin D.

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Obesity paradox in colorectal cancer patients: Overweight colorectal cancer patients were 55 percent less likely to die from their cancer than normal-weight patients with the disease, according to a study published in *JAMA Oncology* by Candyce H. Kroenke, ScD, MPH, Bette Caan, DrPH, and colleagues. The study represents the largest cohort of colorectal cancer patients with the most comprehensive data regarding patient weight before, at time of, and following diagnosis. Overweight and obesity have been identified as risk factors for many health conditions, but for people with colorectal cancer, some extra weight may provide protection against mortality, researchers found.

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Immunotherapy for lung cancer: In global clinical trials, patients with advanced metastatic lung cancer who were treated with a targeted immunotherapy drug lived significantly longer and with fewer side effects than those who received standard second-line chemotherapy, according to a study by Louis Fehrenbacher, MD, medical director of Kaiser Permanente Oncology Clinical Trials, and colleagues, published in *The Lancet*. The use of atezolizumab, a monoclonal antibody, improved the survival rate of a majority of lung cancer patients who had progressive cancer when used after first-line chemotherapy.

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Social integration and breast cancer outcomes: In a large study of women with invasive breast cancer, socially integrated women — those with the most social ties, such as spouses, community ties, friendships and family members — had significantly lower breast cancer death rates and disease recurrence than socially isolated women. This study was published in the American Cancer Society journal *Cancer*, by Candyce H. Kroenke, ScD, MPH and colleagues. Read More

Active surveillance for prostate cancer: Due to concerns about the overtreatment of low-risk prostate cancer, active surveillance is now a recommended alternative to the active treatments of surgery and radiotherapy for appropriately selected men. In telephone interviews with newly diagnosed low-risk prostate cancer patients, researcher Stephen Van Den Eeden, PhD, and colleagues found that 39.3 percent preferred active surveillance, 30.9 percent preferred active treatment, and 29.7 percent had no preference. Although a substantial proportion of men preferred active surveillance, this was associated with anxiety and uncertainty, suggesting a difficult choice. Read More

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Cardiovascular and Metabolic Conditions

Heart disease and statins: While many Americans take statins to protect their heart health, a *JAMA Viewpoint* article by Associate Director Alan Go, MD, and other researchers highlights the need to develop a better understanding of the long-term benefits and risks for the millions of older Americans who are taking statins to prevent a first heart attack or stroke. The researchers call for a randomized clinical trial of statins in older patients without heart disease to understand the balance between benefits and risks. Read More

Predicting diabetes after gestational diabetes: Senior Research Scientist Erica Gunderson, PhD, working with University of Toronto’s Michael Wheeler, PhD, discovered a simple, accurate new way to predict which women with gestational diabetes will develop type 2 diabetes after delivery, using data from Gunderson’s landmark SWIFT study. The discovery would allow health care providers to identify women at greatest risk and help motivate women to make early lifestyle changes and follow other strategies that could prevent them from developing the disease later in life. Read More
Heart attack decline in Northern California: Heart attack rates among an ethnically diverse population of more than 3.8 million Kaiser Permanente members in Northern California fell 23 percent from 2008 to 2014, as reported in the Journal of the American College of Cardiology. The dramatic, ongoing improvements linked to population-based prevention and care build on research published in 2010 in the New England Journal of Medicine that demonstrated a 24 percent decline in heart attacks among Kaiser Permanente members in Northern California between 1999 and 2008.

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Death rates due to heart disease and stroke: Heart disease has been the leading cause of death in the United States since 1921, according to the CDC. Now, after more than a decade of steady improvements, the decline in mortality rates from heart disease and stroke has slowed nationally and nearly leveled out since 2011, according to a new analysis from the Division of Research published in JAMA Cardiology. “Continued innovation is essential in our efforts to address the ongoing challenge of cardiovascular disease prevention,” said lead author Stephen Sidney, MD, MPH.

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Cardiovascular risk tool: Kaiser Permanente Northern California researchers and clinicians have found that a nationally recommended risk calculator for predicting a person’s chance of experiencing an atherosclerotic cardiovascular disease event — such as heart attack, ischemic stroke or dying from coronary artery disease — substantially overestimates actual 5-year risk in adults, overall and across all sociodemographic subgroups within Kaiser Permanente. The study, published in the Journal of the American College of Cardiology, provides critical evidence to support recalibration of the risk equation to current populations in usual clinical care.

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Health Care Delivery and Policy

Predictive analytics and hospital care: Gabriel J. Escobar, MD, and his team developed an early warning tool that analyzes clinical information about patients sick enough to need hospital care but not appearing sick enough to require treatment in an intensive care unit (ICU). Using data from more than 1 million patients of Kaiser Permanente Northern California, the tool accurately predicts which patients are most likely to deteriorate later in the day and require transfer to the ICU the next day. The work was featured by TPMG CEO and Executive Director Robert Pearl, MD, in his Forbes blog.

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Seniors and online health tools: Despite widespread access to online health-care tools among U.S. seniors, digital access and usage preferences differed significantly among seniors by race/ethnicity and age, according to a study by Nancy Gordon, ScD, published in the Journal of Medical Internet Research. The study is believed to be the first to document these racial/ethnic differences in real-world usage patterns and to link them to differences in access and preferences for online health care tools, in a large cohort of seniors enrolled in a large, integrated, health care delivery system.

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Delivery Science fellows: The Delivery Science Fellowship Program, initiated in 2013, aims to train postdoctoral fellows in research on identifying and implementing best practices for delivering care to diverse populations. Led by Richard Grant, MD, MPH, and Julie A. Schmitt, PhD, the program has attracted nationwide interest. Fellows who joined the Division of Research in 2016 were Devon Check, PhD, who is focusing on cancer care delivery; and Hannah J. Jang, PhD, MSN, RN, who is studying nursing care and outcomes. In 2016, the program initiated its first Clinical Informatics Research Fellowship; Samuel Kabue, PharmD, will focus on predictive modeling of medication-related outcomes.

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Lupus awareness program: With funding from the Centers for Disease Control and Prevention and in partnership with the Lupus Foundation of America, this new initiative seeks to improve symptom recognition, diagnosis and health-related quality of life among individuals with lupus. Led by Lisa Herrinton, PhD, the PULSE (Partners United for Lupus Sustainable Education) program will implement an evidence-based national awareness and education campaign; develop a National Lupus Partners Network; and increase the implementation of evidence-based self-management education, physical activity, and strength-training strategies.

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2014-2015 Member Health Survey results: The Member Health Survey is used to describe sociodemographic and health-related characteristics of the adult membership of Kaiser Permanente Northern California and monitor trends over time, identify health disparities, and conduct research. The confidential survey has been conducted triennially by Nancy Gordon, ScD, starting in 1993; the 2014 survey results were posted mid-year. The Member Health Survey has yielded unique insights and provides an opportunity for researchers and public health organizations outside of KPNC to leverage survey-generated statistics and collaborate on epidemiologic and health services research studies.

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Translational research in diabetes care and prevention: Julie A. Schmittiel, PhD, and colleagues received a 5-year renewal for their Health Delivery Systems Center for Diabetes Translational Research from the National Institute of Diabetes, Digestive, and Kidney Disease. The center aims to actively foster and support translational research in diabetes within health care delivery systems affiliated with the Health Care Systems Research Network (HCSRN), the University of California, San Francisco, and safety net hospitals nationally. Investigators affiliated with the Center have published more than 100 papers in the past 5 years, and conducted pilot and feasibility studies to advance community referrals in diabetes and improve diabetes care for children and families.

Caring for complex patients: New research by Richard Grant, MD, MPH, and colleagues seeks to develop innovative approaches for improving the care of complex patients with type 2 diabetes, including the growing number of Latinos. With new support from the Patient Centered Outcomes Research Institute, researchers will evaluate and expand the Spanish-language version of a waiting room tool to support more effective communication between complex patients and their primary care providers. Funded by the National Institutes of Health, another new award will support mentoring and training of clinicians with an interest and passion for patient-oriented research to improve the care of patients with type 2 diabetes.

Infectious Diseases and Vaccine Study Center

Life expectancy gap for HIV patients: The lifespan of HIV-infected individuals has increased dramatically with combination antiretroviral therapy, yet a gap in survival persists when compared to individuals without the virus, according to a Division of Research study published in the Journal of Acquired Immune Deficiency Syndromes. In 1996 to 1997, life expectancy among HIV-infected individuals was only 39; by 2011, an HIV patient could be expected to live to age 73. However, a gap in life expectancy persists, ranging from 8 to 13 years.
Tdap booster effectiveness: Research by the Vaccine Study Center, published in *Pediatrics*, found that the Tdap booster vaccine provides moderate protection against whooping cough during the first year after vaccination, but its effectiveness wanes to less than 9 percent after 4 years among teenagers who have received only a newer form of the whooping cough vaccine (acellular pertussis vaccine) as infants and children. The study explored Tdap effectiveness among adolescents during outbreaks of whooping cough in Northern California in 2010 and 2014.

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Safety evaluation of vaccination schedules: In collaboration with Brigham and Women’s Hospital, the Vaccine Study Center has received funding from the National Institute of Allergy and Infectious Diseases to develop a wide variety of new epidemiological methods for studying the safety of childhood vaccination schedules, including the timing of individual vaccines, the timing between doses of the same vaccine, and the interaction effects of different vaccines given on the same day.

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Substance use disorders in HIV population: With funding from the National Institute on Drug Abuse, and in collaboration with University of California, San Francisco, the Division of Research will develop and test the delivery of interventions to improve health outcomes of people living with HIV with substance use disorders. The intervention will be delivered in advance of routine health care visits, and aims to systematize substance use disorder screening aided by use of patient portals, within several large HIV clinics in Kaiser Permanente Northern California.

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HIV patient enrollment after Affordable Care Act: A study examining enrollment by HIV-positive patients in Kaiser Permanente Northern California after ACA implementation found an increase in HIV-positive patient enrollment and improvement in HIV viral control. HIV-positive patients also had high rates of comorbid medical, psychiatric, and substance use disorders that pose a challenge to providing effective care. However, the long-term effects of shifts in patterns of comorbidity, growth in Medicaid, and increased selection of higher deductible plans remain unknown.

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Women's and Children's Health

Gestational diabetes postpartum intervention: The Gestational Diabetes' Effects on Moms (GEM) trial, led by Assiamira Ferrara, MD, PhD, and colleagues, compared the effectiveness of diabetes prevention strategies at the health system level to address postpartum weight retention for women with gestational diabetes mellitus. During the first year after birth, women in the intervention were significantly more likely to meet weight goals and increase vigorous-intensity physical activity than women in usual care. Read more

Ovarian cancer prevention: A surgical procedure recommended to reduce the future risk of ovarian cancer was successfully implemented throughout Kaiser Permanente Northern California without a change in surgical outcomes, according to research published in Obstetrics and Gynecology by senior author C. Bethan Powell, MD, and co-author Tina Raine-Bennett, MD, MPH. The study showed the results of widespread adoption of salpingectomy following the development and implementation of a systemwide education program on the procedure. Between June 2013 and May 2014, 72.7 percent of women included in the study had fallopian tubes removed at the time of hysterectomy, compared with 14.7 percent between June 2011 and May 2012. Read more

Perinatal depression screening: A universal screening program implemented in Kaiser Permanente Northern California increased the number of women diagnosed and treated for depression during and after pregnancy and resulted in significant relief from their symptoms, according to two Kaiser Permanente studies published in Obstetrics and Gynecology by Tracy Flanagan, MD, and Lyndsay Ammon Avalos, PhD, MPH. Flanagan's team — which received Kaiser Permanente's 2016 James A. Voh's Award for Quality — identified best practices; empowered advocates on site to help educate obstetricians; streamlined the work flow for screening during obstetric office visits; and used data to continuously improve the program. At full implementation, the program screened 98 percent of pregnant and postpartum women at least once during and after pregnancy, and an average of 2.5 times per pregnancy. Read more
Infections, antibiotics and childhood obesity: Infections during infancy — rather than antibiotic use, as previously suspected — were associated with an increased risk of childhood obesity, in a study of more than 260,000 infants published by De-Kun Li, MD, PhD, in *The Lancet Diabetes & Endocrinology*. The study is one of the largest analyses of the interplay among infections, antibiotic use and childhood obesity, and adds important evidence to a small but growing body of research on how the microbiome, or gut bacteria, may be affecting childhood development. Read more

Environment and childhood obesity, neurological disorders: Assiamira Ferrara, MD, PhD, and Lisa A. Croen, PhD, received a major new grant from the National Institutes of Health to study how exposures to environmental chemicals during pregnancy may influence the risk of obesity and neurodevelopmental disorders in children. Kaiser Permanente investigators will focus on *in utero* exposures to endocrine-disrupting chemicals — including perfluoroalkyl substances (or PFAs), polybrominated ethers (PBDEs), and organophosphate flame retardants (OPFRs) — which are found in many common household and personal products, plastics and furniture. The proposed 7-year study launched with $3.25 million in initial NIH funding over the first 2 years, with an estimated total funding of $24 million. Read more

Pediatric cancer and infant phototherapy: Phototherapy, increasingly used to treat jaundiced infants, could very slightly raise the risk of pediatric cancers, according to research published in *Pediatrics* by Michael Kuzniewicz, MD, MPH, and colleagues at UC San Francisco. The two studies were among the largest to date: one examined about 500,000 babies born at Kaiser Permanente Northern California between 1995 and 2011, the other more than 5 million babies born in California between 1998 and 2007. A slight increased risk of cancer was found in one study but only partly confirmed in the other. The authors said a little more caution was warranted in using phototherapy, especially in babies with Down syndrome. Read more
2016 Financial Report

The Division of Research (DOR) is currently home to about 53 investigators and staff scientists, with more than 600 employees. The DOR also works with 28 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. DOR scientists are involved in nearly 400 research studies. Since its founding in 1961, DOR researchers have published about 3,500 scientific papers, including more than 375 papers in 2016.

2016 Funding Sources Based on Expenditures

- $87 Million Total Expenditures

54% Federal
12% Industry
11% Foundation/Nonprofit
11% The Permanente Medical Group
5% Kaiser Permanente (Other)
4% Community Benefit (Regional)
3% Community Benefit (Central Research Committee)