

# DIVISION OF RESEARCH 2021 Annual Report



Pioneering the Future of Health Care





## Pioneering the Future of Health Care

One hundred years ago, innovations in medicine and health care changed the way we think about the world and how we treat patients today. In 1921, the tuberculosis vaccine was first used on humans, Congress passed a law to reduce the then-high rates of maternal and infant mortality, and researchers in Toronto announced the discovery of insulin.

The pioneers behind those efforts helped shape how medicine and health care advanced. But they likely could not have begun to imagine how our own pioneers at the Division of Research would improve the health and well-being of Kaiser Permanente members.

These pioneers include people like **Gabriel Escobar**, whose risk calculator made possible the **Advance Alert Monitor**, leading to reduced hospital patient mortality. The sophisticated hospital early warning system received recognition with an **international award** in 2021.

Other trailblazers include **Alan Go** and Adjunct Investigator Chi-yuan Hsu, and their colleagues, who received recognition for their work that identified a way to **remove race** from a kidney function equation. Their paper was **cited** by NIH Director Francis Collins and selected by The New England Journal of Medicine as one of its **Notable Articles** of 2021.

Sometimes innovation comes from reassessing commonly held beliefs, such as **Bette Caan's** work questioning the idea that weight gain is crucial to reducing risk of recurrent breast cancer. She identified an "obesity paradox" that retaining muscle mass matters most; she told **Scientific American** magazine this past year: "We can't be stuck in what we thought was true, because then we're never going to move the field forward."

And that's what we do at the Division of Research: move the field forward.

We've developed **tools** to help identify COVID surges, and risk assessments for patients with **chest pain** and other emergency symptoms. **Stacy Sterling's** team in the Center for Addiction and Mental Health Research has created a helpful **tool** for parents to assess their child's risk of substance use. And the Vaccine Study Center, under **Nicola Klein's** leadership, builds on its 30-year reputation for elegant study design and use of data with a key role in the nation's COVID-19 vaccine safety surveillance.

It's not hard to imagine that many of the innovators of tomorrow will have begun their work here at the Division of Research.

In 2021, we drew one of our largest-ever classes of research fellows, adding 7 new **early career investigators** to our postdoctoral research program. Of this new class, 3 are **Delivery Science Fellows**, 1 is an **NIH T32** grant recipient, and another jointly participates in a California epidemiology training program. Together, they cover fields from diet and dementia to cancer and clinical informatics, to women's and children's health, and more.

Innovation is in our DNA at the Division of Research. We can't wait to see what the future holds.



*Tracy Lieu*

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

# 11 BIG RESEARCH STORIES FROM 2021

Projects from across the Division of Research made a splash in 2021. Here are some of the year's attention-grabbing stories:

COVID-19 vaccine trial starts for children  
[Read Story »](#)  
More from *Los Angeles Times*

Mental health treatment rate rose early in pandemic  
[Read Story »](#)  
More from *HealthDay*

Pandemic leads to increased cannabis use by pregnant women  
[Read Story »](#)  
More from *Associated Press*

Method found to remove race from controversial kidney function equations  
[Read Story »](#)  
More from *Healio.com*

New tool for early identification of COVID-19 surges  
[Read Story »](#)  
More from *HealthcareITnews*

'COVID toes' likely not caused by COVID-19, in most cases  
[Read Story »](#)  
More from *Medscape*

Gestational diabetes tip-off to future increased risk for heart disease  
[Read Story »](#)  
More from *US News & World Report*

Continuous glucose monitors help patients manage type 2 diabetes  
[Read Story »](#)  
More from *UPI News*

Improved stomach cancer survival with regionalized care program  
[Read Story »](#)  
More from *MDedge.com*

No serious health effects linked to mRNA COVID-19 vaccines  
[Read Story »](#)  
More from *Medscape*

Stroke rate 4X higher in Black young and middle-aged adults, compared to whites  
[Read Story »](#)  
More from *Cardiology Today*

# Research Highlights



## Behavioral Health and Aging

### Increased cannabis use by pregnant women during pandemic

An analysis of more than 100,000 pregnancies in Northern California found the rate of cannabis use early in pregnancy rose from 6.8% to 8.1% after the start of the COVID-19 pandemic. The analysis was reported in *JAMA* by [Kelly Young-Wolff, PhD, MPH](#), and [Lyndsay Avalos, PhD, MPH](#). “It’s very possible that more pregnant women are using cannabis in an attempt to self-medicate [for stress] during the pandemic,” Young-Wolff said.

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### Teen suicidal thoughts and behaviors varied during pandemic

The number of teens being seen at Kaiser Permanente Northern California emergency departments for suicidal thoughts and behaviors did not increase significantly during the first few months of the COVID-19 pandemic, according to research in *JAMA Psychiatry* led by [Kathryn Erickson-Ridout, MD, PhD](#), and [Esti Iturralde, PhD](#). However, increases were seen for subsets of patients, such as teen girls.

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### Problems for teens who stop taking ADHD medication at adulthood

Teens diagnosed with attention deficit hyperactivity disorder (ADHD) often don’t take their medication regularly, and Kaiser Permanente research indicates the problem gets worse when they approach adulthood. Adolescent psychiatrist [Kavitha Rao, MD](#), worked with research scientist [Cynthia Campbell, PhD, MPH](#), on an analysis published in the *Journal of Adolescent Health* that found adherence to filling prescriptions among ADHD patients dropped to 19% at age 19.

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### Genetic clues for increased risk of age-related cataract

An analysis led by [Hélène Choquet, PhD](#), and published in *Nature Communications* identified new locations on the human genome that were associated with the risk of age-related cataract, including a finding specific to women, who get cataracts more often. A better understanding of the genetic underpinnings of cataracts can lead to the development of tests to identify individuals at greater risk so they can get earlier treatment, Choquet said.

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## Biostatistics Core

### Air pollution increases risk of death from heart disease and stroke

A meta-analysis of results reported in 69 papers found long-term exposure to fine particulate matter (PM2.5) pollutants increased the risk of death from coronary artery disease by 23% and from stroke by 24%. The study led by [Stacey Alexeeff, PhD](#), is the first to quantify and compare the effects of long-term exposure to these pollutants on risks for these heart problems. The study was published in the *Journal of the American Heart Association*.

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### \$5.6 million awarded to Kaiser Permanente researcher to study treatments for type 2 diabetes

A research team co-led by [Romain S. Neugebauer, PhD](#), received a \$5.6 million funding award from the *Patient-Centered Outcomes Research Institute (PCORI)* to study the benefits – and potential harms – on heart health of medications used to treat type 2 diabetes. Said Neugebauer, “We are very excited to... generate solid evidence that patients and providers can use to help reduce their risks of cardiovascular and other diabetes-associated complications.”

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## Cancer

### Spinal fractures tied to bone metastases

A study published in [JAMA Network Open](#) highlighted why researchers who follow breast cancer survivors over time should differentiate between fracture types. “As we began to study fracture outcomes in this group it became clear we needed to separate fractures which were pathologic – meaning caused by the cancer – and fractures which were likely related to bone fragility,” said the study’s lead author [Joan C. Lo, MD](#).  
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### Assessing prognosis for metastatic colorectal cancer

Research published in the [Journal of Clinical Oncology](#) found an association between p53 mutations and survival based on the anatomical location of the tumor. “We had expected gain-of-function mutations to be associated with worse survival,” said lead author [Minggui Pan, MD, PhD](#), “but that wasn’t the case with right-sided colorectal cancers.” If the results are confirmed, the findings could aid researchers assessing treatments in clinical trials and help physicians treat patients with colorectal cancer.  
[Read More ▶](#)

### Racial disparities in breast cancer therapy use

Women who identified as American Indian or Alaska Native were less likely than women of other racial and ethnic groups to start hormone therapy for breast cancer after surgery and stay on the treatment for the recommended 5 years. “The disparities we found indicate that further research is needed on modifiable factors that contribute to adherence that might differ by

race and ethnicity,” said senior author [Laurel Habel, PhD](#). The study was published in [Cancer](#).

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### Studying colorectal cancer screening

[Theodore R. Levin, MD](#), is co-leading a team of researchers from the DOR and Dartmouth that will compare the risks and benefits of an annual fecal immunochemical test (FIT) to colonoscopy for colorectal cancer screening in adults over 70 who have previously been diagnosed with small, low-risk polyps. The study was made possible through a \$32.7 million funding award from the Patient-Centered Outcomes Research Institute. “We hope to understand whether older people with small, low-risk polyps can safely opt to use the non-invasive FIT for surveillance,” said Levin.

[Read more ▶](#)

### Beyond body mass index

[Elizabeth Cespedes Feliciano, ScD, SM](#), and [Bette Caan, DrPH](#), published a study in the [American Journal of Clinical Nutrition](#) on the association between abdominal adipose tissue radiodensity and survival after colorectal cancer. Caan’s research was also featured in a [Scientific American](#) documentary. “There was such a belief that it was weight gain that was important in overall cancer survival,” Caan explained. “But now ... we have learned that overweight or mild obesity is associated with an improved outcome or no worse outcome than people who are in the so-called normal range.”

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## Cardiovascular and Metabolic Conditions

### New insights on worsening heart failure

A study led by [Andrew P. Ambrosy, MD](#), that used artificial intelligence and natural language processing to scan electronic medical records found the number of patients in the hospital with worsening heart failure was 2 times higher than what was observed relying only on primary discharge diagnoses. This research

creates an opportunity to identify these high-risk patients more accurately. The study was published in [JAMA Network Open](#).

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## Cardiovascular and Metabolic Conditions (Continued)

### Removing race from kidney function equations

A study published in the [New England Journal of Medicine](#) contributed to efforts to address possible race discrimination in medicine. “Our research showed that if you use a blood cystatin C test, instead of a blood creatinine test, you don’t need to include race to get a similarly accurate estimate of kidney function,” said co-senior author, [Alan S. Go, MD](#), and co-lead author [Chi-yuan Hsu, MD, MSc](#), a DOR adjunct investigator.

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### Emergency care for heart attacks and strokes rebounds

The significant declines in heart attack hospitalizations and emergency care for possible strokes seen in Northern California at the beginning of the COVID-19 pandemic were not seen in subsequent surges, researchers reported in [JAMA](#). The research team, which included lead author [Matthew D. Solomon, MD, PhD](#), and co-author [Mai N. Nguyen-Huynh, MD](#), said the findings suggested efforts to reassure patients that it was important to leave their homes and seek emergency care, if needed, were successful.

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### Racial disparities in stroke

Research published in [Hypertension](#) that used data collected in the [Coronary Artery Risk Development in Young Adults \(CARDIA\)](#) study found that the stroke rate was 4 times higher in Black young and middle-aged adults, compared to whites. “This study confirms that it’s not only whether you have high blood pressure but how long you have had high blood pressure and how long the damage to the blood vessels has been occurring that matters,” said senior author [Stephen Sidney, MD, MPH](#).

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### Gestational diabetes is marker for heart disease risk

Research scientist [Erica P. Gunderson, PhD, MS, MPH](#), led a study that found women with a history of gestational diabetes are at increased risk for heart vessel calcification, a marker of increased risk for heart disease, throughout their childbearing years and into mid-life, even if they currently have normal blood sugar levels. The study was published in [Circulation](#).

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## Clinical Trials

### COVID-19 vaccine trial for children

The Vaccine Study Center, led by [Nicola Klein, MD, PhD](#), headed Kaiser Permanente Northern California’s participation in the Pfizer/BioNTech’s COVID-19 vaccination trials for children aged 5 to 11, enrolling children at 3 medical centers. “Children and adolescents may benefit from having protection from COVID-19 so they can return to school, sports, and other activities safely,” said Klein.

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### Early remdesivir to prevent progression to severe Covid-19 in outpatients

In a study in [NEJM](#), co-author [Jacek Skarbinski, MD](#), and colleagues, with support from the KPNC Clinical Trials Program, showed that remdesivir improved outcomes for patients hospitalized with COVID-19. “These data add yet another option to the armamentarium for the treatment of vulnerable patients who are at high risk for progression to severe Covid-19,” wrote the authors.

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Continued on page 8

## Clinical Trials (Continued)

### GUARD-AF and atrial fibrillation screening

The ReducinG stroke by screening for Undiagnosed atrial fibrillation in elderly individuals (GUARD AF) study aims to determine if earlier detection of atrial fibrillation through one-time screening in previously undiagnosed men and women at least 70 years of age in the U.S. ultimately impacts the rate of stroke, compared to usual standard medical care. The importance of this study, which [Alan Go, MD](#), helps lead and recruit through the Division of Research, was the subject of an NIH workshop report coauthored by Go in the [Journal of the American Heart Association](#).

[Read More ▶](#)

### No serious health effects linked to mRNA COVID-19 vaccines

The Vaccine Study Center, led by [Nicola Klein, MD, PhD](#), reported in [JAMA](#) that no serious health effects could be linked to the COVID-19 vaccines through June 2021. Klein called the initial results of the Vaccine Safety Datalink rapid cycle analysis “reassuring.” “The world is relying on safe and effective vaccines to bring an end to the COVID-19 pandemic,” she added. “The Vaccine Safety Datalink is ideally suited to carry out this important surveillance and we will continue to monitor the safety of all vaccines that protect against COVID-19.”

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## Delivery Science

### Patient-reported outcomes in head and neck cancer

Patient-reported outcome surveys that are integrated into an electronic medical record can help oncology care teams quickly address the treatment-related symptoms and side effects head and neck cancer patients experience. “Prompt symptom management can improve a patient’s short- and long-term quality of life,” said the study’s senior author [Jed Katzel, MD](#). “It can also reduce hospitalization and emergency room visits during cancer treatment.” The study was published in [JCO Clinical Cancer Informatics](#).

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### Artificial intelligence can help improve care for people with heart disease

Teaching computers how to read written notes in medical reports could make it easier for doctors and health systems to track and manage patients with aortic stenosis and other chronic heart conditions. The study, published in [Cardiovascular Digital Health Journal](#), showed that a computer taught to intelligently recognize certain abbreviations, words, and phrases was able to identify nearly 54,000 patients with aortic stenosis. The study was led by [Alan Go, MD](#), and [Matthew Solomon, MD, PhD](#).

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### COVID toes were likely not caused by COVID-19, in most cases

In the midst of the pandemic, an unusual number of patients began reporting the red, itchy toes that are the hallmark of chilblains. Many initially assumed it was a symptom of COVID-19. But research led by [Patrick McCleskey, MD](#), suggested the increase in chilblains was more likely related to behavior changes that occurred during the pandemic – not the coronavirus. “The media attention to ‘covid toes,’ along with general anxiety about COVID, likely led more people to contact their doctor,” said the study’s senior author, [Lisa Herrinton, PhD](#). The study was published in [JAMA Dermatology](#).

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### Blood clot risk low in non-hospitalized COVID-19 patients

COVID-19 patients who are not hospitalized are at low risk of developing blood clots and should not routinely be prescribed blood thinners, a [JAMA Internal Medicine](#) research letter suggested. “It was recognized within the first months of the pandemic that patients with COVID-19 were having more blood clots in the hospital and in the intensive care unit than other patients who were similarly ill,” said adjunct investigator [Nareg Roubinian, MD](#), the study’s first author.

[Read More ▶](#)

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## Delivery Science (Continued)

### Personalized care for patients with chest pain

Research led by [Dustin G. Mark, MD](#), and [Mary E. Reed, DrPh](#), showed that a KPNC-developed risk-assessment tool provided doctors with a more accurate way to assess how likely it is a patient who comes to the emergency department with chest pain will have or die from a heart attack, stroke, cardiac arrest, or other major heart-related problem within the next 60 days. The study was published in the [Journal of the American Heart Association](#).

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### Mental health treatment rate rose early in pandemic

A detailed analysis of mental health treatment trends during the COVID-19 pandemic published in [The Journal of Clinical Psychiatry](#) found a 7% increase in visits during the initial shelter-in-place period in 2020, compared with the same 3-month period in 2019. “The increases we found in patients seeking care for substance use and anxiety are consistent with other data showing the pandemic and shelter-in-place orders were difficult for many people,” said lead author [Kathryn Erickson-Ridout, MD, PhD](#), who co-authored the analysis with [Esti Iturralde, PhD](#), and colleagues.

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## Health Care Delivery and Policy

### Similar follow-up after telemedicine and office visits

Patients who made appointments to see their primary care doctors by video or phone did not seek substantially more follow-up care than those who had traditional in-person visits, found research led by [Mary Reed, DrPH](#), and published in [JAMA Network Open](#). The results suggested virtual visits can address a person’s concern comparably to in-person care.

[Read more ▶](#)

### Predictive model, case management reduced readmissions

A predictive model identifying hospital patients at risk of a readmission developed by [Gabriel Escobar, MD](#), was paired with a case management team of registered nurses and social workers in the Transitions program. An analysis published in [BMJ](#) found Transitions reduced readmissions without increasing mortality.

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### New tool for early identification of COVID-19 surges

[Vincent Liu, MD, MS](#), and DOR’s Systems Research Initiative team developed a predictive model using data from routine clinical care that could identify the onset of upcoming COVID-19 surges as many as 6 weeks before they occur. Using 10 clinical indicators, the COVID-19 HotSpotting Score (CHOTS) significantly increased the lead time to spotting a surge. Their work was published in [BMJ Open](#).

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### Continuous glucose monitors for type 2 diabetes

A study led by [Andrew J. Karter, PhD](#), found that in patients with insulin-treated type 2 diabetes prescribed a continuous glucose monitor by their doctor, the monitor’s use was associated with better blood sugar control and fewer visits to the emergency room for hypoglycemia. The study was published in [JAMA](#).

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## Health Care Delivery and Policy (Continued)

### Pandemic increased mail order pharmacy use

Research published in [Diabetes Care](#) found that mail order pharmacy use increased during the COVID-19 pandemic among adults with type 2 diabetes, but use continued to differ by race and ethnicity. Before the pandemic started in March 2020, 8.4% of the study participants had a prescription filled through the mail order pharmacy, reported lead author [Tainayah Thomas, PhD](#), and senior author [Julie Schmittiel, PhD](#). By September 2020, the number rose to 31.8%. [Read More ▶](#)

### Regionalized care for stomach cancer

Research published in the [Journal of Clinical Oncology](#) showed that a regionalized, virtual gastric cancer program improved outcomes for stomach cancer patients by making it faster and easier for KPNC oncologists to introduce leading-edge cancer treatments. “The regionalized gastric cancer program combines the benefits of community-based care, which is local and convenient, with the expertise of a specialized cancer center,” said co-author [Lisa Herrinton, PhD](#). [Read More ▶](#)



## Infectious Diseases

### HIV prevention treatment showed gaps

A large, detailed look at patients taking HIV prevention drug therapy found strong adherence soon after patients got the prescription but less consistent use thereafter, particularly among groups considered high priority for receiving the medication. The study, led by research fellow [Carlo Hojilla, RN, PhD](#), with co-author [Michael Silverberg, PhD, MPH](#), was published in [JAMA Network Open](#). [Read More ▶](#)

### Kaiser Permanente data key to nation’s COVID-19 vaccine surveillance strategy

The Vaccine Study Center, led by [Nicola Klein, MD, PhD](#), became a key part of the nation’s COVID-19 vaccine surveillance strategy when it was chosen by the CDC to carry out a rapid cycle analysis tracking serious reactions among patients of the [Vaccine Safety Datalink](#). “The Vaccine Safety Datalink is the premier system in the United States, and arguably in the world, for active, real-time safety surveillance of vaccines,” Klein said. [Read More ▶](#)

### Higher risk of dementia for older adults living with HIV

A study using patient data across 3 Kaiser Permanente regions found nearly double the rate of dementia among people with HIV compared with those without HIV. The research was led by [Jennifer Lam, PhD](#), with co-authors [Catherine Lee, PhD](#), [Paola Gilsanz, ScD](#), [Derek Satre, PhD](#), and [Michael Silverberg, PhD, MPH](#), and published in the journal [AIDS](#). The patients were all on antiretroviral therapy and their dementia was assumed not to be related to HIV. [Read More ▶](#)

### People with HIV at increased risk of heart failure

A large study of people with HIV who were members of 3 Kaiser Permanente regions from 2000 to 2016 found they were more likely to have heart failure than a comparison group of similar people without HIV. The study was published in [Mayo Clinic Proceedings](#) and led by [Michael Silverberg, PhD, MPH](#), and [Alan Go, MD](#). “With this study, we now see the cardiovascular impacts for people with HIV extend to end-stage conditions such as heart failure,” Silverberg said. [Read More ▶](#)



## Women's and Children's Health

### Healthy lifestyle linked to lower risk of preterm birth

A combination of 3 healthy lifestyle factors is associated with 70% lower risk of preterm birth, according to an analysis of data from nearly 2,500 pregnant women by [Yeyi Zhu, PhD](#), and [Assia Ferrara, MD, PhD](#), published in [The American Journal of Clinical Nutrition](#). Women whose weight, diet, and stress were in healthy ranges had lower risk of preterm birth than women who did not have those factors in healthy ranges.

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### Kaiser Permanente researchers study pandemic pregnancies

Women's and children's health section investigators began publishing studies using data from a unique survey of pregnant members of Kaiser Permanente Northern California about their experiences living through a pandemic while pregnant. The survey was developed by co-principal investigators [Lisa Croen, PhD](#), and [Assiamira Ferrara, MD, PhD](#). [Jennifer Ames, PhD](#), and Croen published in [PLOS One](#), finding higher prevalence of COVID-19 infections among younger pregnant women and those living in neighborhoods with greater economic deprivation.

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### No link between autism and common antidepressant when used in pregnancy

A study by [Jennifer Ames, PhD](#), and [Lisa Croen, PhD](#), published in the journal [Biological Psychiatry](#), confirmed previous research that suggested SSRI antidepressants used before and during pregnancy are not associated with increased risk of autism and other neurodevelopmental disorders in children. The analysis offered new insights by including a large and demographically diverse group of mothers and children and looking at specific subgroups of children.

[Read More ▶](#)

### Pregnant women using cannabis live closer to retailers

Pregnant women who lived near recreational cannabis retailers in California were more likely to use cannabis early in their pregnancies, found research led by [Kelly Young-Wolff, PhD, MPH](#), and published in [JAMA Network Open](#). "What's important is that we provide universal health education about the potential risks of prenatal cannabis use and empower women to make informed decisions about cannabis use during pregnancy," Young-Wolff said.

[Read More ▶](#)

### Longtime women's health study SWAN tackles the challenges of aging

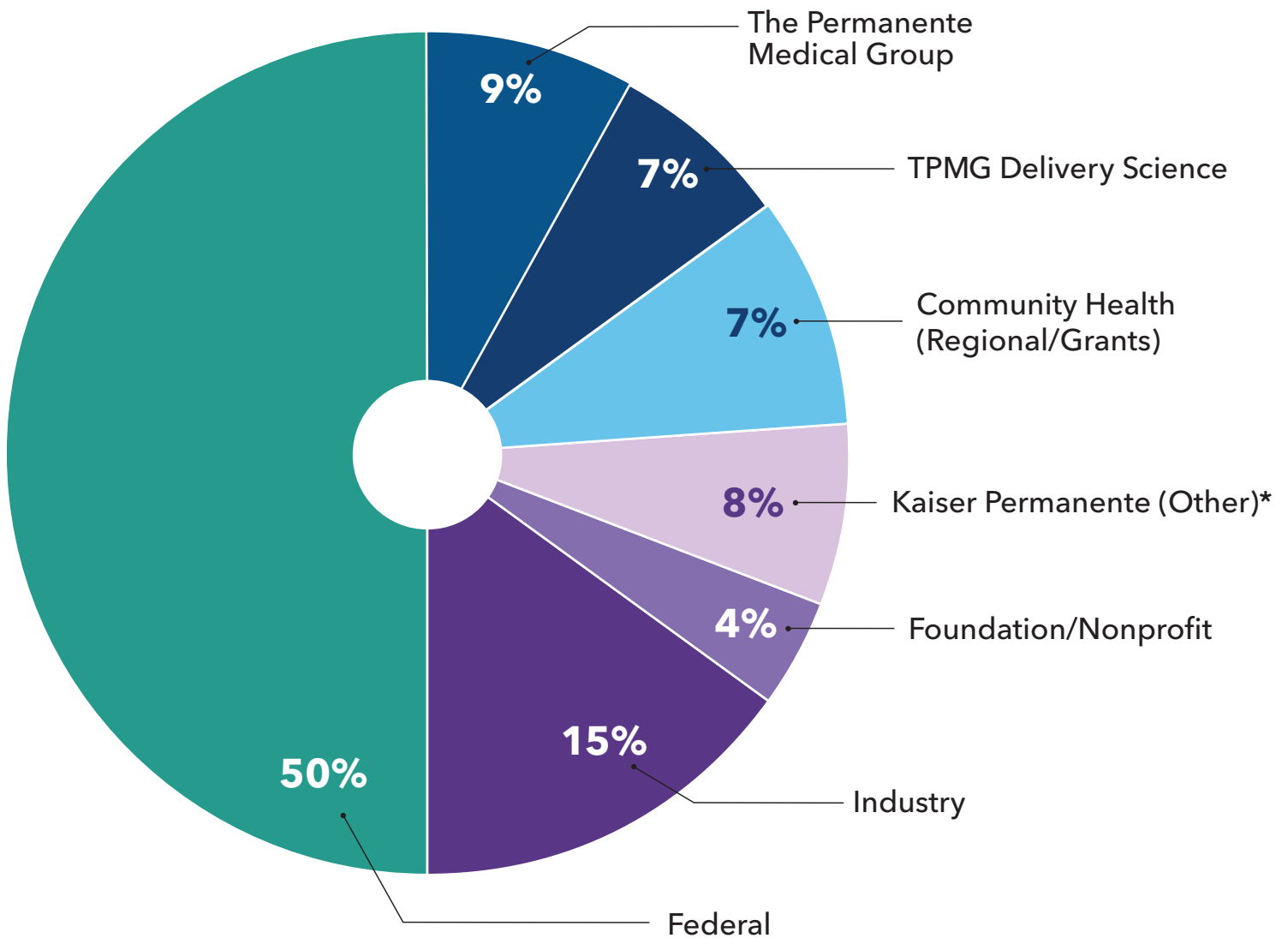
[Monique Hedderson, PhD](#), became the third DOR investigator to lead the local site of the [Study of Women's Health Across the Nation \(SWAN\)](#), planning a focus on hormonal changes and symptoms during the menopause transition. SWAN follows a cohort of about 2,500 women of diverse racial and ethnic backgrounds to study their health over time. DOR has managed a study site for 27 years, ever since Emeritus Research Scientist [Barbara Sternfeld, PhD](#), led the local effort with a focus on physical activity. [Laurel Habel, PhD](#), later took over, focusing on breast cancer risk factors.

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# 2021 Financial Report

The Division of Research (DOR) is currently home to **62** research scientists and staff scientists, **13** research fellows, and more than **630** employees. The DOR also has **48** adjunct investigators from within Kaiser Permanente and other academic institutions. DOR's scientists are involved in **587** ongoing research projects and its Clinical Trials Program supports and guides **372** clinical trials. Since 2000, DOR researchers have published more than **6,000** peer-reviewed articles, including **580** papers in 2021 alone.

## 2021 TOTAL REVENUE: \$136 MILLION



\*(Incl. CESR, Garfield, KP Biobank, etc.)

# Leadership Team

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