

SYNTHESIS

THE MAGAZINE OF UC DAVIS COMPREHENSIVE CANCER CENTER VOL 18 • NO 1 • SPRING/SUMMER 2015



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MESSAGE FROM THE DIRECTOR

Dear Reader,

If we are to reduce the number of lives lost to cancer today and into the future, we must do our jobs better. That means intensifying our ability to characterize individual tumors and developing treatments tailored specifically to them. It also means making the treatments we already have safer for patients and preventing new cancers in the first place.

In this issue of *Synthesis*, we explore two very different projects that take aim at the toxicity that can go along with certain diagnostic tests generally and with cancer treatment specifically.

In one, you will learn about Diana Miglioretti, who combs large databases of patient data to look for any associated risk with cancer and a child's exposure to medical radiation, such as computed tomography. In another, you'll meet Megan Daly and Yoshihiro Yamamoto, who are working on technologies to home in on a tumor with radiation therapy in a moving lung without damaging critical functional tissue.

Synthesis also will introduce you to two exceptional individuals who have recently brought their expertise to UC Davis and who will help us expand our research enterprise: Kate Rauen, an expert in certain pediatric genetic mutations also found in many cancers; and Bradley Pollock, public health epidemiologist with a focus on pediatric cancer.

You will also meet Yvonne Wan, a nationally known liver researcher who studies imbalances in gastrointestinal bacteria (microbiota) that can contribute to gastrointestinal and liver cancer. Her basic research may also yield clues to the role healthy bacteria play in preventing these cancers.

Finally, we introduce a growing cadre of oncology professionals who work in our clinics and our hospital: nurse practitioners. These advanced practice nurses not only facilitate access for patients by extending the reach of oncologists, but help provide patient-centered care and improve cost-effectiveness.

We hope you enjoy this issue of *Synthesis*.

RALPH DE VERE WHITE

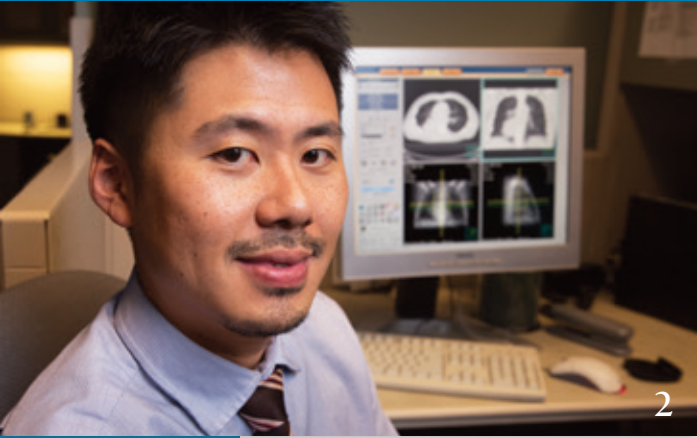
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Breaking Barriers to Beat CancerSM

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CANCER CENTER

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comprehensive cancer center*

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Homing in on a moving target

New mapping strategy designed for lung cancer therapy

Radiation treatments have a simple goal: zap cancer cells until they die. But there's a downside.

While clinicians make every effort to precisely target radiation and hit only tumors, these treatments invariably affect healthy tissues, leading to debilitating, occasionally deadly, side effects. As a result, radiation oncologists must limit doses to spare patients.

This is no small problem. Lung cancer is one of the deadliest malignancies. In 2011, it's estimated there were more than 220,000 new cases in the United States; around 155,000 of those patients will ultimately die of the disease.

Increasing radiation doses could potentially stem this tide. However, safeguarding healthy tissue is especially difficult when treating lung cancer. As patients breathe, tumors become moving targets.

Physicians have been looking for better ways to safely direct radiation at tumors. Now, a group of researchers and clinicians at UC Davis may be close to a solution. The team has developed a unique way to map a patient's lungs, allowing radiation oncologists to provide even higher doses without compromising patient safety.



A moving target

When radiation was first used against lung cancer decades ago, clinicians lacked the imaging technology to track lung movement and were forced to irradiate tumors along their entire path. This treated the cancer but also damaged the lungs.

Sophisticated imaging systems have made radiation oncology safer and more precise. Now, radiation oncologists use computed tomography (CT) scans before treatment to locate tumors and track their movements.

“When a patient gets radiation, there’s a planning session to design the radiation fields,” says

To make radiation **more effective**, radiation oncologists would like to **boost their doses to tumors** without increasing the risk to normal tissue.

Megan Daly, assistant professor in the Department of Radiation Oncology. “We use both a regular CT scan and a 4D scan, which captures the motion of the lungs and the motion of the tumor.”

These scans help the clinical team better target the moving tumor. However, the technology isn’t perfect,

and some radiation inevitably hits healthy tissue, generating a number of health risks. A study conducted in 2013 found that 30 percent of patients treated with both chemotherapy and radiation developed serious lung inflammation, a potentially fatal condition called radiation pneumonitis.

“Patients develop pneumonia-like symptoms,” notes Daly. “They have to be treated with weeks of steroids. In the long run, this can reduce overall pulmonary function and exercise capacity, as well as cause lung scarring.”

Next-level precision

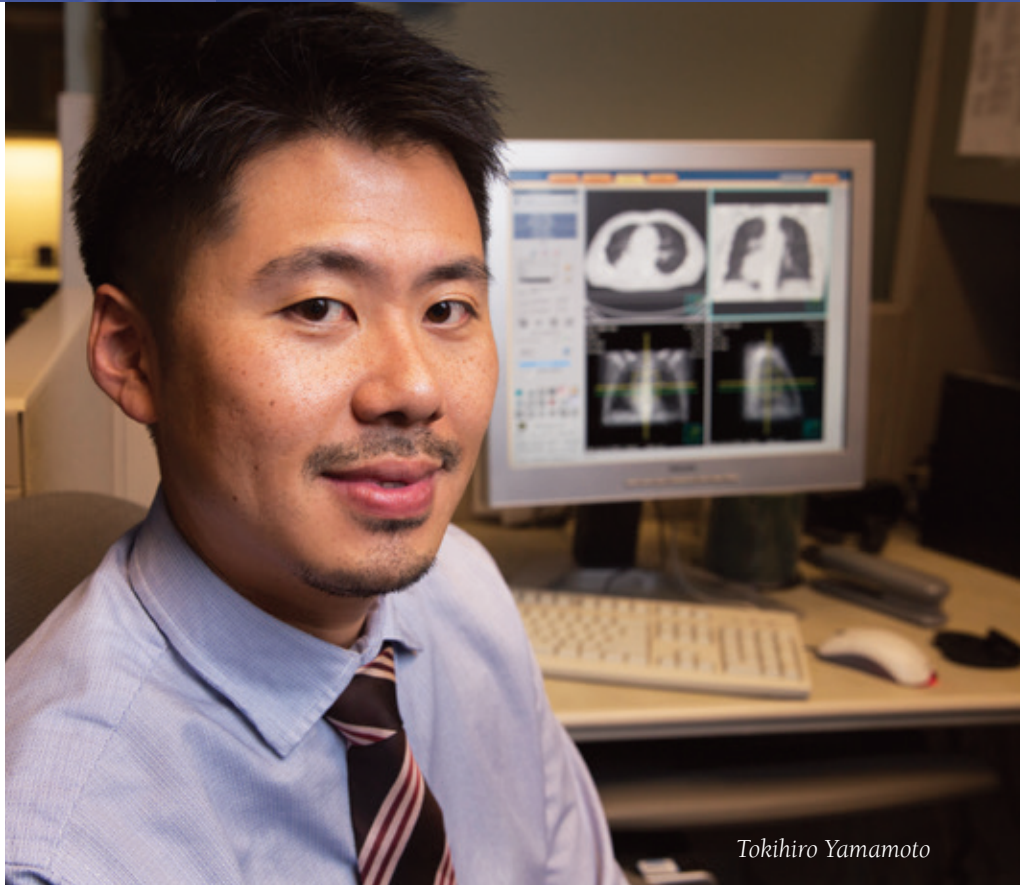
Better imaging technologies and software could offer incremental gains in radiation targeting, but there’s another approach that may provide even greater benefits. All lung tissue is not created equal; some areas are more functional, absorbing more life-giving oxygen.

Selectively hitting less-functional regions could increase patient safety. By measuring function in different parts of the lungs, radiation oncologists could map treatment so that any scattered radiation will strike the less active areas, reducing potential side effects, such as pneumonitis.

This new approach is the brain-child of Tokihiro Yamamoto, assistant professor in the Department of Radiation Oncology. Yamamoto has spent more than five years developing ways to measure lung function around tumors, a process called 4D CT ventilation imaging.

“4D CT images provide a movie of a patient’s lung and tumor motion,” says Yamamoto. “Using advanced image-processing technology, we can use these images to estimate which parts of the lung are functioning and which are not. With that information, we can improve radiation treatment planning and delivery to avoid hitting healthy lung regions with high radiation.”

One of the advantages of this technique is that it does not require any additional scans, re-tasking information that’s already being used



Tokihiro Yamamoto

Yamamoto has spent more than **five years** developing a **new method to measure lung function around tumors – 4D CT ventilation imaging.**

to plan treatment. Yamamoto and colleagues then apply sophisticated algorithms to measure how patients’ lung volumes change as they inhale and exhale. The resulting data helps him map the most functional areas and miss them during treatment.

“We’re hoping that by avoiding these highly functional lung regions,

we will reduce toxicities associated with radiation,” says Yamamoto.

Personalized therapy

The next step for 4D CT ventilation imaging is testing it and designing personalized treatment plans for lung cancer patients. Daly, Yamamoto and colleagues are

In other words, by **measuring function in different parts of the lungs**, radiation oncologists could **map treatment** so that any scattered radiation will strike less functional areas, **reducing potential side effects**, such as pneumonitis.



conducting a small trial to determine whether 4D CT ventilation image-guided radiotherapy is safe.

Each patient will have the functional regions in their lungs mapped so that radiation will preferentially avoid those areas. Although some radiation will still hit normal lung tissue, it will be largely in less-crucial regions. The researchers hope these trials will show this method is safer for patients.

“Inevitably, there is going to be some dose delivered to the lungs,” says Daly. “We’re trying to make sure that dose avoids the most important parts of the lungs.”

While this technology is first being tested for safety, the researchers also will be looking at its effectiveness. Will radiation treatments using 4D CT ventilation imaging do a

comparable job at controlling cancer?

If the results are positive, the method could eventually become part of the normal radiation therapy regimen for lung cancer patients. But it’s a long path.

“This is a Phase I trial, testing for safety and feasibility,” says Yamamoto. “If this is successful, we hope to move on to a larger Phase II in the near future.”

“Inevitably, there is going to be some dose delivered to the lungs. We’re trying to **make sure that dose avoids the most important parts** of the lungs.”

~ Megan Daly



Orchestrating excellence

Nurse practitioners key players in cancer care

When Mafini Tupai was diagnosed with cancer she sought treatment at various cancer centers looking for the right combination of great medicine and great care.

She finally arrived at UC Davis Comprehensive Cancer Center two years ago, and stayed.

A stage-IV breast cancer patient, she felt the providers at other centers had given up on her. It was different at UC Davis, where she said her oncologist, Kendra Hutchinson, “heard my story. I needed someone to fight this with me, and she was willing to do that.”

Hutchinson, however, is only part of Tupai’s cancer

AT LEFT (left to right) Brian Stuepfert, Susan Ferrara, Laura Brennan, Flora Stondell, Brianna Kalmykow, Lewis Ingram, Christine Teklehaimanote, Kathryn Wells

NOT PICTURED Abimbola Olusanya

care team. At her monthly visit, Tupai also sees longtime nurse practitioner Lewis Ingram, who makes sure she is tolerating her immunotherapy and has her pain under control. Along with Hutchinson, Ingram also monitors Tupai and her laboratory tests for any changes in the disease progression.

“Lewis is a people person,” Tupai says. “He is very caring. He listens. He is very attentive. It’s like he’s a male version of Dr. Hutchinson. Even though she is my main doctor, I can trust Lewis to take care of me.”

Ingram is one of nine nurse practitioners taking care of UC Davis cancer patients. Each of them specializes in different cancer types and provides personalized care to patients at the time of diagnosis, during treatment and through survivorship. The involvement of nurse practitioners in the oncology setting, while not new, increasingly is seen as an important component of the cancer care team. These advanced-care nurses facilitate patient access to oncology care, extend the reach of oncologists and provide comprehensive care that improves quality of life for patients.

“It’s often said that medicine is like a team sport,” explains Ted Wun, UC Davis chief of Hematology and Oncology. “The physician may be the quarterback, but all players are vital to the success of the team. I prefer the metaphor of the orchestra; the physician as a conductor of many talented musicians — nurses, nurse

practitioners, pharmacists, social workers and others. If everyone does their individual parts well, but in a coordinated fashion, there is beautiful music. In oncology that means outstanding, patient-centered care. But it takes a lot of teamwork and practice.”

The role of nurse practitioners in oncology care delivery is especially important now as incidence of the disease continues to grow with an aging population. The World Health Organization last spring reported that cancer is poised to become a global epidemic, with cases expected to



NP Lewis Ingram and Mafini Tupai

Ingram is **one of nine nurse practitioners** taking care of UC Davis cancer patients. **Each of them specializes in different cancer types and provides personalized care to patients** at the time of diagnosis, during treatment and through survivorship.

jump 57 percent worldwide over the next 20 years, thereby increasing the demand for oncology services and potentially surpassing the supply of available oncologists.

The oncologist shortage is projected to grow as more providers retire and the demand for cancer diagnosis and care through survivorship increases. The number of cancer survivors alone is expected to surge to 18 million in the United States by 2022.

Cost effectiveness, therefore, is essential in ensuring access to care



95%

OF NURSE PRACTITIONERS
HAVE A GRADUATE DEGREE



97%

OF NURSE PRACTITIONERS
MAINTAIN NATIONAL CERTIFICATION

With more people **surviving cancer** comes a **need to provide specialized post-treatment care** and monitor for recurrences — **a role well suited to nurse practitioners** in both adult and pediatric clinics.

and better outcomes for patients.

“We increase the cost-effectiveness of care by preventing patients from being hospitalized,” says Laura Brennan, a nurse practitioner at the cancer center. “We watch them carefully and take care of things as they come up.”

Special credentials

Abimbola (Abby) Olusanya in surgical oncology decided to become a nurse practitioner because she wanted to contribute to patient care at an advanced nursing-practice level. That meant that she first needed a bachelor’s degree, followed by a master’s of science in nursing. She then became a certified family nurse

practitioner, one of many types of role-specific nurse practitioner certifications. Olusanya also earned a doctorate in nursing.

At the cancer center, Olusanya sees patients before and after cancer surgery. She also coordinates surgical oncology research and often serves as a patient-care bridge between the rotations of resident physicians.

“As a nurse practitioner, I manage patients’ care in collaboration with the attending surgeon,” she says. “The best part of my job is seeing a patient go from being ill and frail to a vibrant and healthy individual who starts planning for life after retirement and/or living long-term. It is a great privilege to contribute to that process.”



“The **best part of my job** is to **see a patient go from being ill and frail to a vibrant and healthy individual** who starts planning for life after retirement and/or living long-term. **It is a great privilege to contribute** to that process.”

~ Abimbola (Abby) Olusanya



Satnam Singh and NP Flora Stondell

Extending care provision

Brennan may be the first person contacted when a patient who has been seen in the clinic needs immediate advice or follow-up care. Like other nurse practitioners at the cancer center, she is especially skilled in caring for acutely ill cancer patients. She can quickly assess a patient's need for a different type of therapy, including chemotherapy and radiation. Or she can arrange for hospitalization of a patient with respiratory distress due to complications of metastasis. She constantly consults with oncologists about individual patient needs.

The oncologist **shortage is projected to grow** as more providers retire and the **demand for cancer diagnosis and care through survivorship increases.**

Colleen Rohde, a registered nurse in the adult infusion center, says nurse practitioners help solve patient emergencies. She cites the time a new patient was getting a blood transfusion, developed a reaction and spiked a fever. Despite the patient being unable to take oral medications such as Tylenol, Rohde worked with nurse

practitioner Christine Teklehaimanote to develop a plan to help the patient through the procedure.

"They are accessible and expedite patient care," Rohde says. "Having them on the team has really streamlined our practice here."

Brennan notes that nurse practitioners also bring a broader

Patient focus>>

perspective to oncology care, taking on longer-term monitoring and medical management of patients, including care designed to keep the patient comfortable.

“Nurse practitioners manage the whole body, which includes palliative care, so we take all those things into

consideration — pain, nutrition, nausea and other side effects of treatment,” she says. “We get to give them hope. We offer them treatment that we hope could extend their life, or allow them to meet a new granddaughter or go to their child’s wedding.”

With more people surviving cancer so comes a need to provide specialized post-treatment care and monitor for recurrences — a role well suited to nurse practitioners in both adult and pediatric clinics.

In the pediatric clinic, for example, nurse practitioner Kathryn Wells developed a special program to monitor young cancer survivors for short- and long-term side effects of cancer treatment that may occur years after treatment. These can include infertility, secondary cancers, emotional or educational problems, and growth and development concerns. The clinic utilizes a computer-based guide that helps Wells and other providers track adolescents and young adults as they transition to adulthood.

A matter of trust

While the presence of nurse practitioners in cancer clinics is becoming more common, not every patient is immediately comfortable with the care model. Even Mafini Tupai was admittedly skeptical, Ingram says.

“When we first met, she was very apprehensive about me and the health-care system,” he says. “But once I developed a relationship with her, she realized that we have her back, and we are watching over her very carefully.”

And that is exactly what Ingram intended when he went into the nursing field 16 years ago.

“I wanted to be able to affect patients’ lives in a positive way,” he says. “It’s a perfect profession for me because I wanted to help others.”



NP Laura Brennan and RN Lailani Rilloque

Brennan notes that nurse practitioners also **bring a broader perspective** to oncology care, taking on **longer-term monitoring** and **medical management** of patients, including care designed to **keep the patient comfortable**.



97%

OF NURSE PRACTITIONERS
CAN PRESCRIBE
MEDICATIONS



11.7

AVERAGE YEARS OF
EXPERIENCE AS A NURSE
PRACTITIONER



6 YRS

ACADEMIC AND CLINICAL
PREPARATION REQUIRED
FOR NURSE PRACTITIONERS

The involvement of **nurse practitioners** in the oncology setting, while not new, increasingly is seen as an **important** component of cancer care teams.

To become a nurse practitioner in California, individuals must have:

- A **bachelor's degree** in nursing
- An **active license** as a registered nurse
- Graduated from a California **nurse practitioner graduate program** that meets Board standards
- **National certification** by an organization whose standards are equivalent to the state's nurse practitioner program standards

Nurse practitioner specialties include:

- Acute Care
- Adult Health
- Family Health
- Gerontology Health
- Neonatal Health
- Oncology
- Pediatric/Child Health
- Psychiatric/Mental Health
- Women's Health

Sub-specialties include:

- Allergy & Immunology
- Cardiovascular
- Dermatology
- Emergency
- Endocrinology
- Gastroenterology
- Hematology & Oncology
- Neurology
- Occupational Health
- Orthopaedics
- Pulmonology & Respiratory
- Sports Medicine
- Urology



RN Amber Svardal and NP Brian Stuepfert

To scan or not to scan?

Researcher moves to make medical imaging safer

It's a typical scenario: a young woman comes to the emergency department because of excessive vomiting and pain in her right lower abdomen.

She is examined and whisked off for a computed tomography (CT) scan, revealing an enlarged, inflamed appendix. Surgery ensues, and the patient goes home a few days later, having been cured of a potentially deadly condition.

"There is no doubt that when radiographic imaging is medically necessary, the benefits outweigh the small risks from radiation exposure," says Diana Miglioretti, Dean's Professor in Biostatistics and a member of the UC Davis Comprehensive Cancer Center. "My efforts are directed at reducing the unnecessary exposures wherever they may occur."

Miglioretti, who has recently been funded for three large research projects aimed at understanding and reducing radiation risk from medical imaging, is directing her sharp focus on determining whether



Diana Miglioretti

unnecessary exposures are occurring, how dangerous they may be, and what can be done to reduce them.

Miglioretti is particularly interested in the surge in CT imaging since it became widely available a few decades ago, with an estimated 75 million scans conducted annually nationwide. The technology generates crisp three-dimensional images that allow differentiation of tissues that vary in density by less than 1 percent, enhancing the diagnosis of a host of conditions from tumors to fractures to internal bleeding. But Miglioretti cautions that the sharp images come with potential for harm: CT scanning exposes a person to up to 500 times the radiation of a conventional chest X-ray.

Miglioretti and collaborators at Kaiser Permanente Northern California and UC San Francisco were recently **awarded a \$10.5 million, five-year grant** from the National Cancer Institute to study **the effects of medical radiation exposure on children.**

Focusing on pediatric cancers

About 4 million CT scans are conducted annually on children in the United States. They are speedy and convenient, and neither doctors — nor parents — want to risk missing a medical

problem that should be addressed. But Miglioretti especially worries about this population of children, who, compared to adults, are most vulnerable to the long-term effects of radiation because of their rapid growth and their longer remaining lifespans.

Miglioretti and collaborators at Kaiser Permanente Northern California and UC San Francisco were recently awarded a \$10.5 million, five-year grant from the National Cancer Institute to study the effects of medical radiation exposure on children. Using large databases from Group Health Cooperative, based in Seattle, Wash., and from three Kaiser Permanente regions, the research team will tally cumulative radiation exposures from medical imaging — before birth and throughout childhood — for some 7.3 million children over a 20-year period. They will search for any associated risk with the development of childhood cancers, particularly leukemia, one of the most common pediatric cancers and one that could theoretically result from radiation exposure to active bone marrow. Leukemia is easiest to study because it has the shortest lag time from radiation exposure to onset.

“We have an ideal study population and data infrastructure to do this important study,” Miglioretti says. “Because the electronic databases at

When Miglioretti started delving deeply into the world of medical imaging, she was shocked to discover that **radiation exposure from the same type of scan can vary dramatically**, depending on both **the machine and its operator**.

each participating HMO have complete capture of all the care their enrollees receive, we can accurately estimate each child’s cumulative medical radiation exposure. This provides the best way to detect cumulative and long-term effects of tests, which on average carry a very low risk to an individual.”

She notes that while two other studies with similar aims have been published, they were based on counting the number of CT scans done on children and estimating the radiation exposure using a calculated average dose per scan. In contrast, the data that Miglioretti and her collaborators will use provide the actual

radiation doses received by each individual. Miglioretti’s earlier research demonstrated that radiation doses can vary greatly across children, even for the same type of imaging test of the same anatomic region. These prior studies have been criticized because of potential confounding factors (e.g., Down syndrome, which might increase both use of CT imaging and cancer risk), and reverse causation (i.e., children may have received the CT exams because of early cancer symptoms); her study will carefully control for these potential biases.

Optimizing delivery

When Miglioretti started delving deeply into the world of medical



“Our studies aim to **systematically find the most effective strategies**, along with the most **efficient ways of disseminating** that information.”

~ Diana Miglioretti



imaging, she was shocked to discover that radiation exposure from the same type of scan can vary dramatically, depending on both the machine and its operator. No standardized protocols for CT scanning exist nationally, and although software designed to optimize dosages for different tests is available, many users opt not to buy it because of the expense.

Two additional research projects are underway to address protocols for CT scanning — a \$6.2 million study funded by the National Cancer Institute, and a \$1.9 million study funded by the Patient-Centered Outcomes Research Institute (PCORI). Miglioretti and her colleagues will collect detailed data to assess current practices, then develop and implement strategies to standardize and optimize CT protocols across a large number of clinics and hospitals in the

But Miglioretti cautions that the **sharp images come with potential for harm**: CT scanning exposes a person to **up to 500 times the radiation** of a conventional chest X-ray.

United States, Canada and the United Kingdom.

“We have seen dramatic results from just discussing standardized protocols with medical physicists and radiologists in a single group meeting,” Miglioretti says. “Our studies aim to systematically find the most effective strategies, along with the most efficient ways of disseminating that information.”

Determining the optimum radiation dosages for a particular purpose can be extremely complex, she adds. The amount of radiation needed depends on the question the clinician is trying to answer; more may be needed to make an initial diagnosis than to track changes in a lesion already identified, for example. In addition, one size does not fit all; small, thin people need less radiation than large, heavy people, who require more radiation to penetrate more tissue. Children need even less.

A statistician’s perspective

Miglioretti realizes that as a statistician she looks at the problem of radiation exposure from a somewhat different angle than does an emergency department doctor or radiologist. When faced with a

patient with a potential medical problem, it is natural to turn to the best test available to obtain a diagnosis if the risk of the test to the patient is low. But the risk, she emphasizes, should not be ignored, given the very large numbers of exams performed.

She wants to convince clinicians that CT imaging should not be used “just to be safe” if it is unlikely to reveal information that would change how a patient’s symptoms are managed. Ultrasound imaging, which does not use radiation, should be considered as an alternative in some situations, at least as an initial test. Ultrasound for conditions such as abdominal pain, for example, often provides results definitive enough to diagnose the problem and eliminate the need for the higher-exposure CT scan.

“Guidelines and policies for medical tests such as CT imaging consider average exposures and associated risks, but as a statistician, I worry about variability across patients,” she says. “Who are the people at the high end of the distribution getting the highest exposures? What effects might radiation have on them? What can we do to bring those high exposures down?”

With three large research grants now underway, Miglioretti is looking forward to digging into the data and finding answers.



Gut reaction

Finding cancer clues in the microbiome

In the past few years, researchers have been gradually illuminating the secret lives of gastrointestinal bacteria, also called microbiota.

This is no small task. There are trillions of microbes in the body — ten times more bacteria than there are cells. And while many may perform beneficial tasks, others aren't so friendly. Researchers believe these bacteria play a role in metabolism, immunity, even mental health. There's also evidence that certain gut bacteria can influence the risk of developing cancer.

Conditions like type 2 diabetes and obesity can skew this carefully balanced system, increasing levels of hostile bacteria. But it may not even take a disease to throw bacterial ratios out of whack. New evidence suggests that the so-called Western diet — high in sugar and fat — also plays havoc with our microbiota.

Could these bacterial imbalances be contributing to gastrointestinal and liver cancers?

Yu-Jui Yvonne Wan, vice chair for research in the Department of Pathology and Laboratory Medicine, and colleagues are on a mission to find out. They want to determine exactly what role bacteria play in gastrointestinal and liver cancers. But even more importantly, if imbalances in gastrointestinal bacteria raise the risk for cancer, could restoring that balance be the key to preventing it?

The busy liver

That gut bacteria might modulate the risk of liver cancer is not as farfetched as it may seem. While



Yu-Jui Yvonne Wan

the liver is rightly credited with filtering out many of the toxins people put in their bodies — alcohol being the most notable — that’s only part of the story. The liver and digestive tract are constantly interacting, transporting fluids, nutrients, fat and bile acids, which are crucial to nutrient absorption and other functions.

“The liver carries a heavy load — detoxification, nutrient absorption, fat metabolism,” Wan says. “Plus, it

They want to determine exactly **what role bacteria play in gastrointestinal and liver cancers**. But even more importantly, if imbalances in gastrointestinal bacteria raise the risk for cancer, **could restoring that balance be the key** to preventing it?

Building on basics>>

has an extremely close relationship with the gut. Bile acid is made in the liver, circulates to the gut and then comes back to the liver.”

This transaction is of particular interest to Wan and could be the point at which bacteria make their entrance. The liver produces water-soluble, or primary, bile acid, which

is transported to the gut. Once there, certain species of bacteria convert this primary bile acid into secondary, water-insoluble, bile acid, which can be toxic.

“In normal amounts, secondary bile acid helps absorb nutrients,” notes Wan. “But everything is about dose. Too much secondary

bile acid can damage DNA and activate cancer genes. It also plays a role in inflammation, which can also be carcinogenic.”

A healthy gut regulates the levels of secondary bile acid; however, there is evidence that people with diabetes, obesity and metabolic syndrome tend to have too many of the wrong bacteria. It’s possible these conditions, and the high-fat diets that help generate them, are creating too much toxic bile acid.

The final straw

Livers are complicated and so is liver cancer. Generally, liver cancer patients have had a previous liver condition, such as hepatitis or fatty liver disease, which ultimately leads to cancer. However, some people can have these pre-existing conditions without developing liver cancer.

Researchers have wanted to explain this disparity. What is protecting some people from cancer while others succumb? Once again,



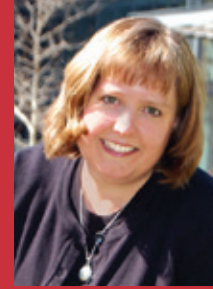
“Bile acid may not be directly causing liver cancer, but there’s a lot of evidence that it plays a contributing role.”

~ Yu-Jui Yvonne Wan

PROJECT TEAM MEMBERS



DAVID MILLS | Mills will study the microbiome and whether supplementation with a particular bacterium typically present in the intestinal tract of infants, together with certain complex sugars present in bovine milk, will have a protective effect against liver and intestinal cancer.



CAROLYN SLUPSKY | Slupsky will be measuring the metabolic difference between normal mice and mice that are genetically lacking bile acid receptors in their liver and intestine. By taking this measurement in the context of a high-fat diet, researchers will learn more about the role bile acids play in cancer development and whether certain intestinal microbes can reverse or prevent it.

the trail leads back to microbiota. It's possible that unfriendly bacteria, which may generate too much toxic bile acid, are the final elements that push fatty liver disease and other conditions into becoming liver cancer.

"Bile acid may not be directly causing liver cancer, but there's a lot of evidence that it plays a contributing role," says Wan.

To figure that out, Wan was recently awarded a \$2.7 million grant from the National Cancer Institute. She and fellow grantees Carolyn Slupsky and David Mills, associate professor and professor, respectively, in the UC Davis Food Science and Technology Department and the Foods for Health Institute, will now have the resources to thoroughly investigate the relationship between gut bacteria and both gastrointestinal and liver cancers.

Building on earlier studies, the team hopes to illustrate the relationship between the Western diet, gut bacteria, metabolism and bile acid. With this information, the researchers believe they will produce a better picture of the entire chain of events that lead to liver and gastrointestinal cancers: diet leading to unbalanced gastrointestinal bacteria; increased production of toxic bile acids; inflammation and DNA damage; and cancer gene activation.

Bacteria as medicine

The research will perform another important function: evaluate potential therapies that could disrupt this chain and perhaps even prevent cancer. With all the cross-talk between gut and liver,

the possible relationship between unbalanced microbiota and liver cancer provides an intriguing possibility. What if we could rebalance gut bacteria to reduce levels of toxic bile acid?

The idea that we can improve health by introducing friendly bacteria is not new. Probiotics have been touted for their health benefits for many years. More recently, doctors have been using fecal transplants to insert beneficial bacteria into diseased intestines to treat *C. difficile*, a bacterial infection that's often hard to treat.

Wan and her team also are interested in using bacteria as medicine. Specifically, they will be testing whether a common gut

microbe, called bifidobacteria, along with oligosaccharides (carbohydrates) found in milk, can restore bacterial balance. The bifidobacteria will enrich healthy gut bacteria, while the oligosaccharides will provide food for these good bacteria. The researchers hope this combination will provide a one-two punch, protecting both the liver and gut from inflammation, reducing levels of toxic bile acid, and lowering the risk of gastrointestinal and liver cancers.

"We want to understand the link between bacterial composition and cancer," says Wan. "But even more importantly, we want to use this approach to intercept the carcinogenic process and, hopefully, reduce cancer formation."

The research will perform another important function: **evaluate potential therapies** that could disrupt this chain and **perhaps even prevent cancer.**

Chatting with Brad Pollock

CHAIR OF THE UC DAVIS DEPARTMENT OF PUBLIC HEALTH SCIENCES

Q: Your work has taken you in a variety of fascinating directions. Can you share some highlights?

A: Most of my career has focused on pediatric oncology research. That includes pediatric cancer epidemiology as well as cancer control research. I've also spent a lot of time on survivorship research, which is very important for childhood cancer. It's great that we now cure most kids, but we have to worry about the downstream effects of their treatment. Certain drugs we use to cure leukemia, for instance, can cause heart failure later in life. Radiation for girls with Hodgkin's disease increases their risk of eventually developing breast cancer. So I've done a lot of work to either prevent those late effects of cancer therapy or treat them to reduce the severity.

I've also spent a lot of time looking at the etiology of childhood cancers. And while we've had many large grants to conduct

national studies on this, we really haven't identified a risk factor that explains any large proportion of childhood cancers. So that's still an important focus.

Q: What sparked your interest in public health and epidemiology?

A: It was really an accident. I applied to medical school in 1977 but didn't get in, so I wound up in the epidemiology program at UCLA. I intended to eventually attend med school but found epidemiology exciting. There were some very interesting things happening in public health at the time. In particular, I remember a doctoral seminar taught by Mike Gottlieb, an immunologist on the faculty, about this group of young gay men with Kaposi's sarcoma. As it turned out, he was documenting HIV and the beginning of the AIDS epidemic. So this medical detective business looked pretty fascinating, and I never left the field.

Q: How does your public health expertise intersect with the mission of the UC Davis Comprehensive Cancer Center?

A: The premise of public health is prevention. So we try to operate on the front end and keep people healthy to reduce their risk of succumbing to cancer. A lot of it focuses on reducing risk by improving people's lifestyle and diet, encouraging them to exercise, and reducing hazardous exposures.

There's also the whole area of biostatistics, which is absolutely critical for any kind of research and the design of clinical trials. Cancer informatics is another key piece of the puzzle, and I've been part of some of the growing national dialogue on that. This is about trying to structure our clinical data in a way that will both promote good research and improve patient care at the bedside.

I also run a large grant called the NCI Community Oncology Research Program, or NCORP. So in that role I'll have an active hand in helping to grow our pediatric oncology program and develop more research.

Finally, Ralph (de Vere White, cancer center director) would like to strengthen our focus on cancer etiology, so we will be recruiting cancer epidemiologists with a molecular-genetic focus.

I've also spent a lot of time on **survivorship research**, which is very important for **childhood cancer**. It's great that we now cure most kids, but we have to worry about the **downstream effects of their treatment**.



Q: Before coming to UC Davis last year you worked at the University of Texas Health Science Center. What differences have you noticed between the two institutions?

A: A major attraction of UC Davis was the fact that it has an integrated health system. This is a really big deal and often underappreciated. The medical school that I came from in September did not own any hospitals. We had affiliations with several local hospitals, but their administrations were not necessarily perfectly aligned with the medical school, and that presented real challenges.

At UC Davis, it's all one health system with a single central electronic

A major attraction of UC Davis was the fact that it has an **integrated health system**. This is a really big deal and often underappreciated.

health record system. That's important to researchers like me to help us develop intelligent systems for medical decision-making and decision support. This will move us toward the concept introduced by the Institute of Medicine called the Learning Health Care System.

Other great features are the leadership at Davis and the fact that it is such a positive environment. The culture of the place is very collaborative and supportive at all levels. Those are really important attributes for building a research program and being successful.

Chatting with Katherine Rauen

CHIEF OF THE DIVISION OF GENOMIC MEDICINE IN THE UC DAVIS DEPARTMENT OF PEDIATRICS

Q: Your research has focused on a set of fairly common medical genetic syndromes. What are they?

A: My work revolves around a group of genetic syndromes called RASopathies, a term I coined and is now used worldwide. These syndromes are caused by mutations in a very important signaling pathway called the Ras/MAPK pathway. It regulates cell growth, which is critical for normal fetal development and, when dysregulated, can cause cancer.

Q: What are the clinical implications for patients who have these syndromes?

A: When you are born with a RASopathy, it's not uncommon to have problems with your heart. Also common are problems in brain function and with your skin, and you are more susceptible to cancer. The first RASopathy

identified was neurofibromatosis type 1. More recently, several [cousin syndromes have been identified, such as Noonan, Costello and CFC syndromes, to name a few. Individually, they are still considered rare, but when you look at these syndromes as a group, you see that more than one in 1,000 people worldwide are born with a RASopathy.

Q: Can you explain the relationship between RASopathies and cancer research?

A: The Ras pathway has been a focus in cancer research for decades, because Ras mutations are found in about 30 percent of cancers, including colon, lung and brain cancers. Most cancer clinicians and researchers are focused, as they should be, on cancers that may develop later in life. What makes RASopathies so important in relation to cancer is that they give us a rare opportunity to look at a

signal pathway in development, because people are born with the genetic mutation in every single cell of the body. So they really allow us to broaden our horizons, learn about the biologic function of the Ras pathway and more about these genes, and ultimately develop better therapies. It's sort of like looking at treatments for cancer by coming in through the back door.

Q: What's your role with the UC Davis Comprehensive Cancer Center?

A: My area of study is Ras biology in development, so it's a natural fit with the cancer center. I'm really glad I've been accepted as a member and that everyone here has embraced the RASopathies. Although the RASopathies involve dysregulated Ras and/or its pathway components, I am interested in how dysregulated Ras affects development early on, and how this can lead to cancer in the future. The fact that Dr. de Vere White (director of the UC Davis Comprehensive Cancer Center) and his team embraced the RASopathies was exciting. They understood the importance of studying Ras, not only from the standpoint of cancers that develop later in life but also from the standpoint of cells with genetic material that can be passed on.

UC Davis is a younger medical center campus, and has many strengths. It's a gem, really, and I think it's beginning to harness its strengths, develop critical mass and build momentum.



Q: You came from a medical powerhouse, UC San Francisco, and you've been at UC Davis for a little over a year. What's your take on the health system and its potential?

A: I am a product of the UC system, and all UCs have their particular strengths and are powerhouses in their own way. UC Davis is a younger medical center campus, and has many strengths. It's a gem, really, and I think it's beginning to harness its strengths, develop critical mass and build momentum. Two examples: no other UC can do telemedicine like Davis, and it's very strong in EHR (electronic health records). Those strengths are going to be critical to the future of genomic medicine.

Genomic medicine is here to stay, and it's barreling down on us like a freight train. So we not only **need to engage future physicians and healthcare providers**, but our current providers.

Q: It's a new year. What's your vision for 2015?

A: It took me awhile to get the lay of the land, but now I'm eager to move genomic medicine forward — not just in pediatrics, but in every aspect of medicine. Genomic medicine is here to stay, and it's barreling down on us like a freight train. So we not only

need to engage future physicians and healthcare providers, but our current providers.

So 2015 for me is really about moving forward at light speed to spread genomic medicine throughout the health system, and provide the best and most innovative care possible to our patients.

Taking life's work a step further

Lung cancer specialist plans large gift

David Gandara has devoted nearly his entire professional career to revolutionizing the treatment of lung cancer.

He will continue that contribution to lung cancer treatment long after his career ends, with the help of a trust he and his wife, Diane Gandara, have established for thoracic cancer research.

“My wife, Diane, and I decided to make this bequest to UC Davis because we believe in the work the cancer center is doing, and we want to make our own contribution to this effort,” the professor and physician explains.

“When we pass, we want a significant amount of our trust to go to this research effort,” says Diane, adding that she and her husband established the trust “as a way to give back to UC Davis.”

It's not as though David Gandara hasn't already given significantly to the cancer research community. For more than 20 years, he has been director of Thoracic Oncology at what is now the UC Davis Comprehensive Cancer Center. For the bulk of that

time he has served as associate director of clinical research. Gandara has witnessed and contributed significantly to the growth of the cancer center and its subsequent designation as a comprehensive cancer center by the National Cancer Institute.

Gandara says he is immensely proud of the stature that the cancer center has attained. And the research currently going on at UC Davis is “extremely exciting,” he adds.

“The UC Davis Comprehensive Cancer Center is still relatively young, but already it has advanced at a faster pace than any other cancer center in the history of the National Cancer Institute in terms of reaching a designation of comprehensive status, which is very prestigious and a small club of the best cancer centers in the country,” explains Gandara. “But we have done so on a very limited budget by comparison with other centers.”

The Gandaras' trust — the amount

of which they prefer not to disclose — is to be designated as a current-use fund for the Thoracic Oncology program. Such a designation allows a considerable portion of the funds to be used on an ongoing basis.

Ongoing access is critical because Gandara and his colleagues are now at the forefront of genetically targeted drug therapies for lung cancer, which are garnering international attention.

“This is an extremely exciting time because of the recent discoveries in cancer molecular profiling. We now have distinguished a large number of genetically-defined subsets of lung cancer, many of which are actionable by new therapies and for which we now have predictive biomarkers,” explains Gandara.

“So that's also important in terms of this gift, because in the future we will have even more to offer our patients. UC Davis can be a leader in this effort, but only if we have the expertise and the financial resources at our disposal to unravel the biologic complexities of this disease,” he adds.

Diane Gandara says she hopes the gift will inspire others to make similar donations, especially for lung cancer research, a disease she says often is not as frequently singled out for private donations.



David and Diane Gandara

Gandara views the bequest as both a way to show his loyalty to the Thoracic Oncology program and to continue his legacy.

“I hope that this bequest Diane and I are making will result in important advances and allow the program to do what it needs to do to continue its success,” he says.

“Whether it is purchasing new equipment, hiring new people, or sustaining research laboratories — things that will allow UC Davis to continue to be one of the top thoracic oncology programs in the country.”

“This is an **extremely exciting time** because of the recent discoveries in **cancer molecular profiling**. We now have distinguished a large number of **genetically-defined subsets of lung cancer**, many of which are actionable by **new therapies and for which we now have predictive biomarkers.**”

~ David Gandara

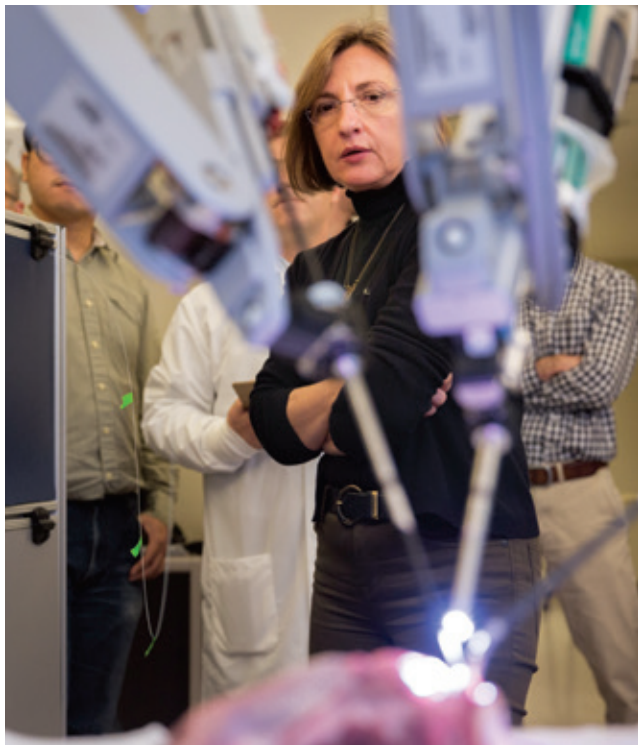
NCI awards UC Davis \$1.5 million to innovate robotic surgery for head and neck cancers

The National Cancer Institute (NCI) has awarded UC Davis \$1.5 million to adapt UC Davis-developed biophotonic technology to a robotic surgical device in hopes of dramatically improving the precision of head and neck cancer surgery.

Developed by Laura Marcu, professor of biomedical engineering and neurological surgery, the device attaches to the da Vinci® surgical system, enabling the robot to scan and assess tissue. **This helps the surgeon distinguish in real-time the difference between normal and cancerous tissue during head and neck cancer surgery.**

“Right now the da Vinci system is very useful for accessing hard-to-reach tumors in the head and neck, but there’s no technology to provide real-time feedback of the tissue type,” Marcu said. “The only way to get information is to order a pathology report, which is not feasible when the surgeon has to rapidly decide where to cut.”

“Some tumors are fairly subtle, and the eye is not refined enough to see them during surgery,” explained Gregory



Laura Marcu tests new technology with the da Vinci robot.

Farwell, professor and director of head and neck oncology and microvascular surgery.

Removing cancers in the head and neck is complex because they are located in functional areas such as on the tongue and close to the voice box. Farwell said he hopes adaptation of the robot to state-of-the-art optical biopsy technology will be the key to addressing this critical challenge.

Working with the company that pioneered the da Vinci surgical system, Marcu is integrating her fiber-optic wand technology into one of the robot’s surgical arms. Farwell will apply the technology in squamous cell carcinoma patients to guide the removal of the tumor during surgery. The device uses laser light to excite molecules within tissues to “read” with pinpoint accuracy the biochemical status of tissue without the need for contrast agents.

Marcu anticipates the technology will be ready for clinical evaluation in less than a year.

UC Davis designated a Lung Cancer Screening Center

UC Davis Health System has been endorsed by the American College of Radiology as a designated lung cancer screening center, the only one of its kind in the greater Sacramento area.

The designation means that UC Davis has complied with stringent quality and safety requirements for its computed tomography (CT) scanning practices, and it confirms that UC Davis meets the required radiation dose standards.

The federal Centers for Medicare and Medicaid Services recommends CT screening for individuals deemed at high risk for developing lung cancer. Those include men and women over 55 and up to age 80 (depending on the insurance coverage) who have smoked more than a pack of cigarettes a day for 30 years or two packs a day for 15 years.

Since Jan. 1, private insurers must cover screening for people who meet the criteria. The decision was based on results of the National Lung Screening Trial, which determined that low-dose CT screening reduced heavy smokers’ risk of dying from lung cancer by 20 percent compared to screening with chest X-rays.

The UC Davis program uses a multidisciplinary team of radiologists, thoracic surgeons, pulmonologists, pathologists, medical oncologists and radiation oncologists to develop a patient-centered plan for leading-edge lung cancer care. Individuals interested in lung cancer screening will need referrals from their primary-care providers to the UC Davis Department of Radiology.

For more news stories, visit cancer.ucdavis.edu, click on “Newsroom.”

UC Davis research finds walnuts slow prostate cancer growth, among other health benefits

Researchers at UC Davis and other institutions have found that diets rich in whole walnuts or walnut oil slowed prostate cancer growth in mice. In addition,



Paul Davis

both walnuts and walnut oil reduced cholesterol and increased insulin sensitivity. The walnut diet also reduced levels of the hormone IGF-1, which previously had been implicated in both prostate and breast cancer. The study was published online in the *Journal of Medicinal Food*.

“While walnuts are high in fat, their fat does not drive prostate cancer growth,” said lead scientist and research nutritionist Paul Davis. “In fact, walnuts do just the opposite when fed to mice.”

A previous study by Davis found that walnuts reduced prostate tumor size in mice; however, that study did not determine which parts of the nuts generated these benefits — the meat, the oil or the omega-3 fatty acids. If it was the omega-3 fats, the benefit might not be unique to walnuts. Since the fatty acid profile for the soybean oil used as a control was similar, but not identical, to walnuts, more work had to be done.

In the current study, the mice were fed whole walnuts, walnut oil or the walnut-like fat for 18 weeks. The walnuts and walnut oil reduced cholesterol and slowed prostate cancer growth. In contrast, the walnut-like fat did not have these effects, confirming that nut components other than the omega-3s caused the improvements.

The research also demonstrated that walnuts modulate several mechanisms associated with cancer growth.

Although results in mice don't always translate to humans, Davis said his results suggest the benefits of incorporating walnuts into a healthy diet. Other research, such as the PREDIMED human study, which assessed the Mediterranean diet, also found that eating walnuts reduced cancer mortality.

The study was funded by American Institute for Cancer Research (award MG10A001), the California Walnut Board and the KU-Research Professor Program of Konkuk University of South Korea.

Nine-year effort concludes to fund breast cancer endowment at UC Davis

After nine years, the Placer Breast Cancer Endowment reached its goal of \$1.5 million for breast cancer research at the UC Davis Comprehensive Cancer Center.

The effort concluded at an event sponsored by the Association of Commercial Real Estate (ACRE) that drew more than 600 people in the real estate industry from around the greater Sacramento region.

“We are absolutely thrilled,” said Ralph de Vere White, cancer center director. “We owe a debt of gratitude to the selfless women of the Placer Breast Cancer Endowment, who tirelessly fought to fund a position dedicated to breast cancer research at UC Davis.”

De Vere White said recruitment for a physician-researcher to fill the position is underway.

The Placer Breast Cancer Endowment was started by two friends, both of whom had been diagnosed with and treated for breast cancer: Carol Garcia, now mayor of Roseville, and Teri Munger, a public affairs executive who lives in Granite Bay. The organization had initially hoped to complete the endowment by 2010, but the economic downturn took a toll on fundraising efforts.

Garcia credited the late Virgil Traynor of the Auburn Community Cancer Endowment Fund for inspiration to drive the breast cancer endowment effort. Traynor's group fulfilled its mission to fund a basic cancer research chair at UC Davis.

“If not for his connecting us with UC Davis and Dr. de Vere White, we would not have known to do this,” Garcia said. “We are also grateful to Dr. de Vere White and the people at UC Davis. We always knew they were there waiting



Pictured at the ACRE Broker of the Year event to complete the endowed breast cancer chair fund-raising efforts, from left to right: Beth Ruyak, Jeanine Stiles, Laura Tyrrell, Teri Munger, Steve Tyrrell, Carol Garcia, Ralph de Vere White.

for us to succeed and were cheerleaders along the way.”

The Placer Breast Cancer Endowment got a boost from another key member of the group, Laura Tyrrell of Granite Bay, who is still battling breast cancer. Laura and her husband, Steve, were instrumental in getting ACRE to select the Placer Breast Cancer Endowment for its charity to support at the annual Broker of the Year Award event.

Endowed chairs support physician-researchers who not only provide patient care but lead and conduct clinical and translational research that can attract additional National Institutes of Health funds.

California breast density law slow to have an impact

UC Davis researchers have found that half of primary-care physicians are still unfamiliar with the new California breast density law, and many don't feel comfortable answering breast density-related questions from patients. The findings, published in the *Journal of the American College of Radiology*, suggest that primary-care providers need more education about breast density and secondary imaging options.

"Overall, the impact of the breast density legislation probably is not significant if primary-care physicians are not educated or aware of it," said lead author Kathleen Khong, a UC Davis radiologist and staff physician. "We should put some emphasis on educating the primary-care physicians so that when patients ask questions, they can be comfortable in addressing the issues."

The law, which took effect in April 2013, requires that patients whose breast density is defined as "heterogeneously dense" or "extremely dense" (about 50 percent of women) receive written notification. The letter also suggests patients discuss the results with their doctor.

The UC Davis study demonstrated that many of physicians are unclear about what to do with the patient information. As a consequence, the researchers said, it appears that relatively few patients with dense breasts are asking questions about their breast density and its implications.



Kathleen Khong

Lung cancer surgery meets Twitter

UC Davis thoracic surgeon David Tom Cooke, a social media innovator, took his work a step further in March when he opened his operating room to Twitter, the popular social media channel. With the help of public affairs staff, Dr. Cooke's surgery on a 68-year-old Chico woman was documented in real time from the moment of her consent to her waking up from anesthesia. It was the first such "live Twitter" event involving surgery at the UC Davis Medical Center.

The patient, Gwen Box, was diagnosed with early-stage lung cancer. Her tumor was located in her right, lower lobe, a good location for the minimally invasive surgical approach called VATS, or video-assisted thoracic surgery.

Mrs. Box agreed to share her story via Twitter to help get the message out that anyone can get lung cancer, even people who never smoked. She said she had been referred

to UC Davis Comprehensive Cancer Center after months of treatments for pneumonia and a lung infection failed, and tests revealed she had cancer.

To prepare for the event, public affairs staff prerecorded several short videos with Dr. Cooke and members of his surgical team. Topics included the procedure itself, anxiety, surgical preparedness and recovery, as well as the role of pathology for diagnostic analysis and research. The videos and other materials were posted throughout the day of surgery, in addition to the live-action material collected and broadcast in real time.

The tweet team used the handle for the UC Davis Comprehensive Cancer Center, @UCD_Cancer, which has more than 3,600 followers, and the hashtag #UCDVATS. The event also was picked up by some local and Bay Area news outlets.



Dr. David Cooke discusses the procedure with Mrs. Box a day before surgery.

Synthesis is published twice each year by the UC Davis Comprehensive Cancer Center.

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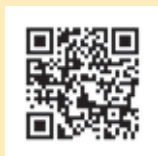
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To commemorate completion of the \$1.5 million endowment for a breast cancer chair, the Placer Breast Cancer Endowment donated this painting by Mya Lauw in a brief ceremony at the cancer center in February. The painting hangs outside the second floor clinic in the North Building.

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Synthesis

Synthesis—the art of bringing together distinct elements in a way that makes them whole — is a particularly

relevant name for the magazine of UC Davis Comprehensive Cancer Center, which is distinct in its commitment to team science.

Our research program unites clinical physicians, laboratory scientists, population specialists and public-health experts from

throughout UC Davis and Lawrence Livermore National Laboratory with the goals of making cancer discoveries and delivering

these advances to patients as quickly as possible. We are also dedicated to sharing our expertise throughout the region,

eliminating cancer disparities and ensuring all Californians have access to high-quality cancer care. *Synthesis*—linking the best

in cancer science toward the united goal of improving lives — is the name of our magazine, and our promise as your National

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