kidney, lung, colorectal, ovarian, and uterine. Liang’s study, which extracted pseudogene expression levels from this data, is part of the TCGA Pan-Cancer Analysis project, an effort to look for patterns across cancer types and genomic dimensions, such as mutations (the genome) and expression levels (the transcriptome).

Liang found that unique sets of pseudogene transcripts were expressed in each form of cancer. In addition, subtypes defined by pseudogene expression levels corresponded closely with subtypes defined by other molecular markers, such as estrogen receptor expression in breast cancer.

In kidney cancer, by joining pseudogene markers with clinical variables, such as disease stage, Liang was able to divide patients into prognostic risk groups. Without pseudogenes, three groups emerge, but adding pseudogenes separates the middle group into two that differ in overall survival. Liang did not investigate the mechanistic roles of pseudogenes, but, he says, “pseudogenes are a novel dimension that we can use to further understand the subtypes.”

“The study included almost 10 times more samples than previous work, which really drives home the validity of the conclusions that pseudogenes can be used as cancer markers,” says Zhang.

Liang hopes to find another large dataset to validate his findings, and also to expand his current analysis across additional types of cancer. “If these patterns are robust, we can consider using pseudogene expression data to build prognostic models that have clinical value,” he says.

### 3D Imaging Finds More Breast Cancers

Adding 3D imaging to traditional digital mammography finds more invasive breast cancers and reduces false positives, a new study finds, although it is not yet known whether the new technology improves breast cancer survival.

Researchers retrospectively reviewed 454,850 mammograms from 13 breast centers. More than a third used 3D imaging, or digital breast tomosynthesis, done at the same time as traditional mammography, whereas the rest used traditional mammography alone.

The invasive cancer detection rate increased from 2.9 per 1,000 traditional mammograms to 4.1 per 1,000 combined 3D mammograms, researchers reported (JAMA 2014;311:2499–507). False positives were 15% less likely using the 3D approach, and there were 16 fewer callbacks for additional imaging per 1,000 screenings.

“Conventional mammography is far from ideal,” says senior author Emily Conant, MD, chief of breast imaging at the University of Pennsylvania’s Perelman School of Medicine in Philadelphia. “3D mammography is an improvement because it addresses two of the major limitations of mammographic screening—there are too many false positives and the sensitivity is not what we’d like, so we miss cancers.”

The FDA approved the Selenia Dimensions digital breast tomosynthesis system (Hologic; Bedford, MA) in 2011 in combination with traditional mammography for breast cancer screening. Using multiple low-dose X-rays taken at different angles, thin “slices” of breast tissue are reconstructed into a 3D image that gives a clearer view of breast tissue.

In an accompanying editorial, Etta Pisano, MD, and Martin Yaffe, PhD, called for more research, noting that it is still uncertain whether tomosynthesis should replace traditional digital mammography (JAMA 2014;311:2488–9).

Conant notes that because the study was not designed to follow women over time, it is not known whether 3D mammography saves lives. It is also unclear which women benefit the most from 3D scans, she says.

“We need research that looks at patient-level data such as breast density, patient age, and the types of cancer detected with 3D mammography that weren’t detected with conventional mammography,” Conant says. “We need to better understand what each woman needs.”

### Improved Survival Ends Nivolumab Trial Early

A phase III trial testing Bristol-Myers Squibb’s (BMS) immunotherapeutic drug nivolumab to treat advanced melanoma was stopped early after the treatment demonstrated a clear improvement in overall survival (OS) compared with standard chemotherapy.

The control group in the randomized, double-blind study—dubbed CheckMate-066—was invited to switch to nivolumab after an independent data-monitoring committee found evidence of superior OS in patients who took nivolumab, BMS reported. The trial was comparing nivolumab 3 mg/kg every 2 weeks with dacarbazine 1,000 mg/m² every 3 weeks in 418 patients with previously untreated BRAF wild-type unresectable late-stage melanoma. It was conducted primarily in Canada and Europe, where dacarbazine is a standard first-line therapy.

“The outcome of CheckMate-066 is an important milestone in the field of immuno-oncology as it represents the first well-controlled, randomized phase III trial of an investigational PD-1 checkpoint inhibitor to demonstrate an overall survival benefit,” says Michael Giordano, MD, head of oncology development at BMS.

Nivolumab is a monoclonal antibody that targets PD-1, a receptor on activated T-cells that inhibits the immune system from attacking cancer cells. BMS is testing the therapy in melanoma, non-small cell lung cancer, and renal cell carcinoma, for which the drug received fast track designation from the FDA last year.

In March, investigators published results from a 107-patient phase I trial showing that nivolumab led to tumor regression and increased OS in patients with advanced melanoma (J Clin Oncol 2014;32:1020–30). The median OS was 16.8 months, with a median response of 2 years among the 33 patients who experienced tumor regressions.
“The apparent durability of clinical activity in nivolumab-treated patients is remarkable,” the authors wrote. “The persistence of partial tumor regressions and stable disease following nivolumab discontinuation . . . suggests that PD-1 blockade may reset the immune equilibrium between tumor and host.”

Investigators will present and publish the results from CheckMate-066 after fully evaluating the data, BMS says. The company also plans to share results with the FDA.

A Plan of Attack for Deadly Cancers

The NCI has released strategic plans for making progress against two of the nation’s deadliest cancers—lung and pancreatic cancers.

The plans were developed in response to the Recalcitrant Cancer Research Act, passed by Congress in 2012, which required the NCI to develop a scientific framework for advances against recalcitrant cancers. Although the Act defined recalcitrant cancers as those with 5-year relative survival rates below 50%, it directed the NCI to first issue reports spelling out research priorities for at least two recalcitrant cancers with 5-year survival rates of less than 20% that are estimated to kill at least 30,000 Americans a year. Lung and pancreatic cancers are the only two diseases that meet this more limited definition.

The scientific framework for small cell lung cancer (SCLC) was issued on July 1; a plan to address pancreatic cancer was released in March.

“I highly doubt that without the Recalcitrant Cancer Research Act we would have seen a small cell lung cancer report,” says Laurie Fenton Ambrose, president and CEO of the Lung Cancer Alliance, a national nonprofit organization that has advocated for a national research plan and will be working with the NCI on its implementation and oversight.

SCLCs account for about 15% to 20% of all lung cancers, and they tend to spread more quickly and resist treatment compared to other types.

The scientific framework identifies five initiatives that could make an impact against SCLC: new tools for tissue collection and tumor models that represent distinct phases of the disease; genomic profiling of SCLC; new diagnostic tests for people at higher risk of developing the disease; molecular-based therapies; and research into factors that define treatment response or resistance. Ambrose expects that the plan will lead to a renewed focus on SCLC research, especially in the areas it highlights.

The scientific framework for pancreatic cancer focuses on research priorities for pancreatic ductal adenocarcinoma, which accounts for 95% of all pancreatic cancers. Priorities include investigating a link between the disease and diabetes; investigating biomarkers for early surgical intervention; developing immunotherapy approaches; and testing treatment strategies that target mutations in KRAS, which are present in 95% of pancreatic ductal adenocarcinomas.

Julie Fleshman, CEO of the Pancreatic Cancer Action Network, a nationwide advocacy group, says that the framework is already leading to new projects and funding opportunities. For example, the NCI has launched a major initiative to target RAS mutations, which “could potentially have a great impact on pancreatic cancer,” Fleshman says.

The frameworks will also help other funding and advocacy organizations complement the NCI’s efforts. The Pancreatic Cancer Action Network, for instance, is launching a fellowship award that will fund a researcher to collaborate with the NCI’s RAS initiative.

Bladder Cancers Respond to EGFR Inhibitors

Muscle-invasive bladder cancer (MIBC) is aggressive, hard to treat, and lethal. Researchers now report they’ve discovered a subtype of the cancer that is vulnerable to EGFR inhibitors.

Although it accounts for about 30% of cases, MIBC causes most bladder cancer deaths. Even after bladder removal, about half of patients die within 5 years. No new treatments for this form of cancer have reached the clinic in more than 20 years, and the heterogeneity of MIBC has posed an obstacle for researchers.

To sort through this diversity, a team led by François Radvanyi, PhD, of the Institut Curie in Paris, France, analyzed gene expression data from 383 MIBC tumors. The researchers found that about a quarter of the tumors fell into a cohesive group that resembled the basal subtype discovered in breast cancer. Clinical data from the patients showed that these “basal-like” MIBC tumors were more deadly than other MIBC tumors.

The basal-like MIBC tumors also revealed a potential vulnerability: They overexpressed genes in the EGFR pathway, including EGFR itself. As the researchers reported in July, the EGFR inhibitor erlotinib (Tarceva) diminished cell proliferation in 9 of 11 MIBC basal-like cell lines, but in only 1 of 11 non–basal-like lines (Sci Transl Med 2014;6:244ra91). The EGFR-targeting antibody cetuximab (Erbitux) also proved effective, particularly in 2 basal-like cell lines where it reduced cell numbers by around 75%.

To test whether erlotinib works in vivo, Radvanyi and colleagues implanted MIBC tumors into mice. Erlotinib curbed the growth of basal-like tumors, but the non–basal-like tumors didn’t respond. The researchers also tested a chemically induced mouse model whose tumors resemble the basal-like growths. Treatment with erlotinib delayed the appearance of the tumors and increased the animals’ survival.

Although previous clinical trials in MIBC patients found that EGFR inhibitors had little effect, Radvanyi notes that these studies included patients with non–basal-like tumors who were unlikely to benefit, which might explain the negative results. The team’s findings also suggest excluding patients with RAS-activating mutations, which render tumors insensitive to the drugs. MIBC “can’t be treated as one disease anymore,” says Radvanyi. “It will be several diseases that are treated separately.”

What makes the result compelling is that “it was comprehensive across all three types of tumor models,” says James McKiernan, MD, of the Columbia University College of Physicians and Surgeons in New York, NY, who wasn’t connected to the study.

If further studies confirm the existence of the basal-like subtype, “it is reasonable . . . to take it to the clinic and see if it works,” says Mark
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