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turns on the JAK–STAT pathway (J Clin Invest 2018;128:402–14).

"It seems that loss of LKB1 in different kinds of cell types can lead to similar types of responses," Ollila says. "It's very important for the field that we ended up at the same conclusion: JAK–STAT signaling is at least one of the key pathways driving the growth of these [benign polyps]."

"What all of these studies are trying to understand is why patients with a heterozygous mutation of *STK11* get polyps," Mäkelä adds. "To me, the question is, 'What is initiating the inflammatory response?'" –*Catherine Caruso* ■

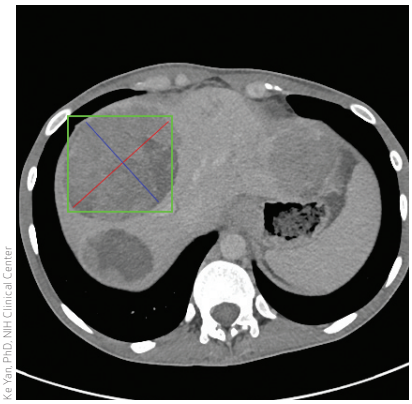
DeepLesion Dataset Aids Tumor Detection

Researchers have long wanted to develop an automated method to detect tumors in medical images. However, gathering enough scans to train a tumor-detection model to accurately recognize lesions using a deep-learning approach has been challenging. Recently, Ke Yan, PhD, a postdoctoral fellow at the NIH, and colleagues compiled DeepLesion, a dataset to address this problem (see nihcc.app.box.com/v/deeplesion). The dataset, which is available for free online, currently consists of 32,120 annotated CT scans featuring 32,735 cancerous and noncancerous lesions of various types, collected from 4,427 unique patients.

In addition to being the largest such dataset available, DeepLesion is also the broadest. "It includes a wide variety of lesion types and locations," says Ronald Summers, MD, PhD, chief of the Imaging Biomarkers and Computer-Aided Diagnosis Laboratory at the NIH Clinical Center and senior author of the paper describing DeepLesion (J Med Imaging 2018;5:036501).

"Many of the existing datasets that have been made public are tailored to specific types of lesions," explains Summers. Thus, the resulting tumor detection models target only one type of lesion, such as lung nodules or colonic polyps. With a broader training set, researchers may be able to develop a single model capable of identifying many tumor types.

Furthermore, tumors pictured in the DeepLesion scans have been measured



Ke Yan, PhD, NIH Clinical Center

A CT scan included in the DeepLesion database shows multiple liver tumors. Red and blue lines bounded by the green box measure one of the tumors using RECIST criteria. An automated method for detecting and measuring lesions could someday determine whether a patient's cancer treatment is working.

by radiologists in accordance with RECIST guidelines. This type of high-quality annotation also sets DeepLesion apart from existing imaging datasets, says Jean-Emmanuel Bibault, MD, of Université Paris Descartes in France. "A major problem with deep learning in medical imaging has been the low quality of image annotation in most image databases. High-quality annotations are crucial for training models."

Summers says his lab will continue adding scans to the dataset and improving software to detect lesions and measure their diameters. However, as the scientific community works to improve tumor-detection models, Summers and Bibault say it will be important to start thinking about how automated tumor detection could be integrated into clinical practice.

"It is not clear how we will clinically validate promising algorithms," notes Bibault. "Should we use randomized clinical trials? If so, should the models be 'frozen,' meaning we don't add any more data to train them? Or should they be continuously updated, so we don't lose one of the advantages of deep learning?"

"We must also consider how automated detection could be implemented in our medical system in a helpful and cost-effective manner," says Summers.

Bibault agrees. "What is the economic model for reimbursement for this kind of algorithm?" he asks. "We simply don't know how it should be done." –*Kristin Harper* ■

With GBM, T Cells May Be Stuck in Bone Marrow

Patients with glioblastoma (GBM) often have low levels of T cells circulating in their blood, and a recent study has uncovered a possible explanation (Nat Med 2018;24:1459–68). These "missing" T cells, researchers discovered, are sequestered within the bone marrow in high numbers instead of being properly trafficked to the blood and lymphoid organs, likely because they lack S1P1, a cell-surface receptor. The findings could lead to more-effective treatments for brain cancer.

Peter Fecci, MD, PhD, of Duke University in Durham, NC, the study's senior author, notes that immunotherapy has so far not worked well against primary brain cancers such as GBM, possibly because these tumor types suppress the immune system. "We started to realize over a decade ago that T cells were potentially missing in these folks, and the ones that are there don't work, and you just can't have an effective immunotherapy without T cells," he says. "My group is focused on trying to understand why that is, with the hope that we can reverse some of those things and take away cancer's ability to sidestep immunity."

Fecci and his team first confirmed that in patients as well as in mice with GBM, there were significantly fewer circulating CD4+ and CD8+ T cells compared with healthy controls. Conversely, they found that this disappearing act correlated with high T-cell numbers in the bone marrow. Moreover, when the researchers implanted other tumor types—including breast, lung, and melanoma—intracranially into mice, they observed a similar bone marrow accumulation of T cells. This did not happen when the same tumor types were implanted subcutaneously.

"What we think we've discovered is a novel mechanism of 'immune privilege'—a way that the brain keeps the immune system out," Fecci says. "These tumors are essentially usurping that mechanism that the brain harbors, and by keeping the immune system away, those tumors are able to thrive."

Next, the researchers determined that sequestered T cells in patients and mice with GBM lacked S1P1; in fact, high bone marrow T-cell numbers

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strongly correlated with low S1P1 levels. Focusing on the mouse models, when S1P1 levels were genetically stabilized, the team observed that T-cell sequestration no longer occurred. Treating these mice with a T cell–activating therapy improved survival, and this was further prolonged by adding the PD-1 inhibitor nivolumab (Opdivo; Bristol-Myers Squibb), which had otherwise not been effective as monotherapy.

Michael Lim, MD, director of the Johns Hopkins Brain Tumor Immunotherapy program in Baltimore, MD, who was not involved in the study, considers it a novel and important finding.

"Everyone is so focused on glioblastomas or any brain tumor causing immunosuppression locally, but this paper highlights this paradigm shift in thinking about the entire body being immunosuppressed," he says. "I think it gives us another strategy in trying to make these tumors responsive to immunotherapy."

Donald O'Rourke, MD, of the University of Pennsylvania in Philadelphia, who was also not connected to the research, considers it "a great step, because it introduces a new way of thinking, and a new avenue for further research."

"In the future, if you were able to give a drug under controlled circumstances where you could encourage T-cell egress out of the bone marrow and into the brain, that would be pretty huge," he says. –*Catherine Caruso* ■

Cervical Cancer Screening Every 5 Years OK

After reviewing the latest data on the benefits and risks of human papillomavirus (HPV) and Pap testing, the U.S. Preventive Services Task Force (USPSTF) has updated its recommendations on cervical cancer screening. They offer many women a new option: screening every 5 years with high-risk HPV testing (JAMA 2018;320:674–86).

"Women between the ages of 30 and 65 now have a choice between three very good options," says Carol Mangione, MD, of the University of California, Los Angeles, who was a member of the committee that developed the recommendations. "They can continue to get a Pap test every 3 years, get high-risk HPV testing every 5 years, or do co-testing, where both tests are performed, every 5 years."

For women who are at average risk for cervical cancer, "the science is very clear—screening every 3 to 5 years is perfectly safe," says Mark Stoler, MD, of the University of Virginia in Charlottesville, who was not involved in developing the recommendations.

"The beauty of these recommendations is that labs are already equipped to perform high-risk HPV testing," he adds. Indeed, many healthcare providers already perform both Pap and HPV tests, so the transition to HPV testing alone should be easy for women who prefer that option.

However, some clinicians and their patients may be skeptical about screening only every 5 years. To them, it may not be obvious why less frequent testing is beneficial. Mangione emphasizes that the USPSTF recommendations consider solely medical risks and benefits, and not costs. Familiarizing healthcare providers with the downsides of screening too often may help promote acceptance of the guidelines. "Screening too frequently leads to harm—mainly too many office visits and too many unnecessary biopsies and other procedures," says Stoler.

For women outside the 30- to 65-year-old age range, cervical cancer screening recommendations remain unchanged. Women ages 21 to 29 should receive Pap tests every 3 years. Groups that do not need to be screened include women younger than 21, and women older than 65 who received three consecutive negative Pap tests or two consecutive negative Pap plus HPV tests in the last 10 years. Finally, women who are at increased risk of cervical cancer—due to a high-grade precancerous lesion, for example—may need more frequent screening.

Although screening is essential for early detection, Stoler emphasizes that driving down the prevalence of cervical cancer will require higher HPV vaccination rates. In the United States, "only half of kids are fully vaccinated, and the goal is 90%," he says. "All the children in this country should get the HPV vaccine." –*Kristin Harper* ■

NOTED

The FDA approved the anti-CCR4 monoclonal antibody mogamulizumab-kpkc (Poteligeo; Kyowa Hakko Kirin) for the treatment of relapsed/refractory mycosis fungoides and Sézary syndrome, two rare forms of non-Hodgkin lymphoma.

Certain germline mutations may increase the risk of triple-negative breast cancer (J Natl Cancer Inst 2018;110:855–62). An analysis of genomic data from 10,901 women with the disease revealed that *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, and *RAD51D* mutations were associated with high risk of triple-negative breast cancer in Caucasian women.

Regeneron Pharmaceuticals and bluebird bio teamed up to develop CAR T-cell therapies, with Regeneron investing $100 million in bluebird. The companies have chosen six initial drug candidates; per the 5-year deal, they will split research costs until a drug reaches clinical trials, at which point Regeneron can opt in 50/50 to continue developing it.

The FDA announced a pilot program to help drug developers use and gain regulatory input on complex innovative trial designs (CID) in their clinical development programs. CIDs include the use of seamless trial designs, modeling and simulations to assess trial operating characteristics, biomarker-enriched populations, Bayesian models, and other novel designs. The agency plans to share CID approaches considered through the pilot program with the broader scientific community.

Human papillomavirus (HPV) vaccination rates among adolescents ages 13 to 17 increased by 5% between 2016 and 2017 (MMWR Morb Mortal Wkly Rep 2018;67:909–17). However, the number of new cases of HPV-associated cancer climbed from 30,115 in 1999 to 43,471 in 2015 (MMWR Morb Mortal Wkly Rep 2018;67:918–24).

Bristol-Myers Squibb's **nivolumab (Opdivo) plus ipilimumab (Yervoy) may be an effective therapy for patients with metastatic melanoma who have untreated brain metastases** (N Engl J Med 2018;379:722–30). In a phase II trial of 94 patients with the disease, 26% had a complete response and 30% had a partial response at a median follow-up of 14 months.

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/CDNews.

AACR American Association for Cancer Research

CANCER DISCOVERY

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