Hospital of Philadelphia and the University of Pennsylvania. For example, in a recently published study, researchers sequenced tumors from 91 children and young adults and found potentially actionable mutations in 46%, some of which triggered changes in treatment (JAMA 2015;314:913–25).

However, the study's authors highlighted significant barriers to delivering appropriate therapies, notes Maris, including a dearth of pediatric clinical trials and often nonexistent pediatric dosing information. As a result, they may be prevented from accessing potentially effective treatments even if an appropriate targeted therapy exists.

"The pediatric oncology community is facing the very urgent issues of defining proper mutation drug matches, making sure they work in the preclinical setting, and figuring out how to get them to children," says Maris. "Routine genetic sequencing and prospective clinical trials in children are the first steps toward breaking down those barriers." –*Janet Colwell* ■

Liquid Biopsy Holds Its Own in Tumor Profiling

According to results from the largest liquid biopsy study to date, the genetic changes detected by analyzing circulating tumor DNA (ctDNA) in blood samples largely reflect those identified through conventional tissue biopsy. The data were presented by Philip Mack, PhD, director of molecular pharmacology at the University of California, Davis, Comprehensive Cancer Center in Sacramento, during the American Society of Clinical Oncology's annual meeting in Chicago, IL, June 3–7.

The investigators used Guardant360 (Guardant Health), a commercially available liquid biopsy that profiles 70 genes, to assay blood samples from 15,191 patients with 50 cancer types. They looked for four classes of genetic changes: point mutations, small insertions or deletions, amplifications, and chromosome fusions. Guardant360's digital sequencing platform "is highly sensitive," Mack said, "which was crucial for our study, because even at very low ctDNA fractions—often below 0.4% of the total DNA in circulation—we were able to detect genetic abnormalities."

Mack reported that the mutation patterns detected via liquid biopsy were "highly consistent" with published tissue biopsy data from The Cancer Genome Atlas (TCGA). In *EGFR*, for example, "the exact same activating mutations reported in tumor tissue by TCGA were observed in our study," he said. When the investigators compared ctDNA sequencing data with matched tissue biopsy results from 386 patients, they found that the former's overall accuracy was 87%, increasing to 98% in cases where blood and tumor samples were collected less than 6 months apart.

The key difference with ctDNA sequencing, Mack added, is that it detected the presence of resistance mutations such as T790M and C797S in *EGFR*. T790M typically emerges as non–small cell lung cancer begins to circumvent erlotinib (Tarceva; Genentech). Although antitumor activity can be restored with next-generation tyrosine kinase inhibitors like osimertinib (Tagrisso; AstraZeneca), secondary resistance mutations, namely C797S, often appear.

"These alterations aren't present in the tumor at the time of an initial tissue biopsy—you'd need follow-up biopsies of metastatic lesions to spot them," Mack explained. "That's still the gold standard, but if you could use plasma instead—and I think our study shows that this is feasible—it would be much less invasive for patients."

Liquid biopsies are "a useful alternative to tissue-based testing, especially for patients with tumors that are challenging to access," said Sumanta Kumar Pal, MD, a medical oncologist at City of Hope Comprehensive Cancer Center in Duarte, CA. "Given the availability of other platforms besides Guardant360, rigorously defining which one provides optimal results will be key." Pal also opined that to fully utilize blood tests in cancer, an oncologist should enroll the patient in a clinical trial like NCI-MATCH or MyPathway.

"A tissue biopsy will always be required upon initial diagnosis to assess the cancer's morphological features," Mack emphasized. "I see ctDNA analyses as having more of a complementary role, mainly for serial assessments of a tumor's evolving sensitivity to therapy as disease progression occurs." –*Alissa Poh* ■

Trial Validates Biosimilar for Trastuzumab

A trastuzumab (Herceptin; Genentech) biosimilar is as safe and effective as its brand-name counterpart for women with HER2-positive advanced breast cancer, according to data presented during the annual meeting of the American Society of Clinical Oncology in Chicago, IL, June 3–7. The findings pave the way for the first FDA approval of a biosimilar for cancer.

In the international Heritage trial, 500 patients with metastatic HER2-positive breast cancer were randomized to receive taxane chemotherapy (docetaxel or paclitaxel) with either the biosimilar MYL-14010 (Mylan) or trastuzumab every 3 weeks for 24 weeks, followed by trastuzumab alone until disease progression.

Women treated with MYL-14010 had a 69.6% objective response rate—the primary endpoint—compared with 64% among women in the trastuzumab arm. The rates of serious adverse events were comparable at 36% (trastuzumab) and 38% (MYL-14010), with neutropenia being the most common.

If approved, the biosimilar could offer a lower-cost alternative to trastuzumab, which has been the cornerstone of therapy for HER2-positive breast cancer, said the study's lead investigator, Hope Rugo, MD, professor of medicine at the University of California, San Francisco, who presented the findings. Investigators will evaluate progression-free survival after participants have completed therapy with trastuzumab alone, she added.

Mylan has already received approval to market MYL-14010 in India, where it is branded as Hertraz. The FDA will consider data both from its use in that country and from the Heritage trial when evaluating the drug's safety and efficacy, said Rugo.

Several other companies—including Pfizer and Amgen—are working on their own versions of trastuzumab, which loses U.S. patent protection in 2019. In addition, ongoing trials are exploring biosimilars of other commonly used cancer drugs, such as rituximab (Rituxan; Genentech) and bevacizumab (Avastin; Genentech).

Thus far, the FDA has approved only one biosimilar: Sandoz's Zarxio (filgrastim-sndz), a biosimilar for

With patent protection on Genentech's blockbuster drug trastuzumab (Herceptin) set to expire in the United States in 2019, several companies, including Mylan Pharmaceuticals, are developing their own versions of the biologic.

Amgen's Neupogen (filgrastim), used to treat neutropenia.

In contrast to generic drugs, biosimilars are not exactly identical to their corresponding brand-name counterparts. Whereas generic drugs are copies of small-molecule drugs with relatively simple chemical compositions, biosimilars correspond to complex large-molecule biologics and must be synthesized from living organisms.

Because biosimilars are impossible to precisely replicate, the FDA requires manufacturers to perform extensive analyses and conduct confirmatory clinical studies demonstrating that the products are highly similar to their branded counterparts, without any clinically meaningful differences.

"This is one of the first trials with biosimilars in oncology to demonstrate similar efficacy, safety, and immunogenicity against the reference product," said Rugo. *–Janet Colwell* ■

Piecing Together the Adrenal Cancer Puzzle

Researchers from 39 institutions in six countries have joined forces to extensively characterize adrenocortical carcinoma (ACC), a rare endocrine cancer that affects just two in every million people worldwide. ACC is often diagnosed at an advanced stage, so its 5-year survival rate ranges from 6% to 13%. Standard treatments for metastatic disease—chemotherapy, radiation, and the hormone-blocking agent mitotane—are palliative and have remained unchanged since the 1970s.

The analysis, part of The Cancer Genome Atlas, was led by Thomas Giordano, MD, PhD, and Gary Hammer, MD, PhD, at the University of Michigan in Ann Arbor; and Roel Verhaak, PhD, at The University of Texas MD Anderson Cancer Center in Houston.

The team used several molecular platforms to scrutinize 91 tumors, including whole-exome and RNA sequencing, and DNA methylation profiling (Cancer Cell 2016;29:723–36). They found that 8% of the samples harbored inactivating *PRKAR1A* mutations—"a new twist in the story," Giordano says, given that alterations in this gene were thought to occur only in benign adrenal disease. They also observed loss of *ZNRF3* in almost 20% of cases, resulting in constitutive activation of Wnt signaling.

"We knew Wnt signaling is important in adrenal cancer biology—some tumors have an initiating mutation in the β-catenin gene [*CTNNB1*], which correlates with poor survival," Hammer explains. "This discovery that *ZNRF3* is a critical mediator adds another level of complexity to Wnt pathway activation." Small-molecule inhibitors of Porcupine, an enzyme that processes Wnt ligands, are in phase I clinical trials for various cancers, he adds, and "we're looking forward to testing their efficacy in ACCs lacking *ZNRF3*."

Additionally, the researchers noted that a sizeable proportion of ACCs displayed evidence of profound genomic instability—often whole-genome doubling, which was associated with more aggressive disease and decreased survival. Why this happens so frequently "is an open mechanistic question," Giordano says.

By clustering their data, the researchers pinpointed three ACC subtypes with different DNA methylation levels: low, intermediate, and high. Statistical analyses showed distinct clinical outcomes—the corresponding tumor recurrence and/or metastasis rates were 7%, 56%, and 96%. The median progression-free survival was not reached in the first subtype; in the intermediate- and high-methylation subtypes, it was 38 months and 8 months, respectively.

"It looks like DNA methylation is a major driver [of the different subtypes]," Giordano observes, "so we're looking to develop this signature into a full, analytically valid prognostic assay." Currently, ACCs are classified as low- or high-grade based on mitotic activity under the microscope, "which isn't all that informative," he adds. "A three-group classification would enable more confident treatment decisions."

Ultimately, "we view our study as more of a hypothesis generator," Hammer says, "and although it's a long road ahead, I think we have the first steps to facilitating targeted therapy development for ACC."

"There's much to do, to better understand all our observations," Giordano agrees, "but the fact that clinical outcome is linked means we're at least barking up the right tree." *–Alissa Poh* ■

FDA Approves Drug Combo for Kidney Cancer

The FDA approved the combination of lenvatinib (Lenvima; Eisai) and everolimus (Afinitor; Novartis) to treat advanced or metastatic renal cell carcinoma (RCC) in mid-May. The approval marks the first time that a tyrosine kinase inhibitor (TKI) and an mTOR inhibitor have been combined successfully as a second-line treatment for patients with RCC whose tumors advance despite previous VEGF-targeted treatment.

"We have been hoping to treat kidney cancer with this type of vertical blockade for some time, but previous combinations have been unsuccessful due to high toxicity," says Ana Molina, MD, a medical oncologist at NewYork–Presbyterian Hospital and Weill Cornell Medicine in New York, NY.

Until recently, oncologists had two second-line treatment options: everolimus and the TKI axitinib (Inlyta; Pfizer). New approvals over the past few months have increased that number to five, including the new lenvatinib–everolimus combination; the PD-1 checkpoint inhibitor nivolumab (Opdivo; Bristol-Myers Squibb); and cabozantinib (Cabometyx; Exelixis), another TKI.

Together, lenvatinib and everolimus have a synergistic effect by blocking multiple points along the VEGF and mTOR signaling pathways that are critical to tumor growth, says Molina. In addition, lenvatinib is a strong inhibitor of FGF receptors, which have been implicated as a potential mechanism of resistance to VEGF-targeted treatments.

The approval was based on a phase II trial in which 153 patients with advanced or metastatic RCC whose disease progressed within 9 months