## **TCGA Report: 4 Subtypes of Stomach Cancer Identified**

he Cancer Genome Atlas Research Network has identified four subtypes of gastric tumors based on shared mutations and other molecular abnormalities. In a report now available online ahead of print in Nature (doi:10.1038/ nature13480), the researchers explain that they analyzed 295 samples of gastric cancer, looking for ways to sort them into groups with similar key DNA defects and molecular aberrations. It was extremely important, they said, to identify categories that would be useful in guiding therapy for patients.

"We clearly converged on four groups of gastric cancer with dis-

tinct features and classes of molecular alterations," Adam Bass, MD, the corresponding author, Director for Translational Research for the Center for Esophageal and Gastric Cancer at Dana-Farber Cancer Center and an associate member of the Broad Institute of MIT and Harvard, said in a news release.

Grouping the cancers in this way will help researchers enroll patients in clinical trials that test drugs designed to target their particular stomach cancer subtype, he said. "There is an urgent need for new therapies because these are aggressive cancers and the fiveyear survival rate is between 20 and 25 percent."

Research on the biology of stomach cancer and the development of new therapies has been difficult because of its diversity and the presence of different pathological forms, he explained. "It is a very heterogeneous disease, but most clinical trials have taken a onesize fits all approach and attempted to find a single optimal therapy to apply across gastric cancer. This traditional



approach has likely contributed to the slow progress we have made in treatments for this cancer."

The team collected fresh, frozen tissue specimens and blood samples from 295 patients from hospitals around the world who had not been treated with chemotherapy or radiation.

The tissue specimens were analyzed with six different molecular analysis technologies, including sequencing the protein-coding DNA in each tumor; detecting mutations or missing or extra copies of gene sequences; determining the methylation status of DNA; sequencing the messenger RNA and microRNA in the tumors; and assessing the expression of key proteins.

When computational methods were applied to the large amount of resulting data, the cancers fell into four subtypes:

• Tumors containing Epstein-Barr virus (EBV), along with mutations in the PIK3CA gene pathway, extreme DNA hypermethylation, and extra copies of PD-L1 and PD-L2 genes. This group made up about 10 percent of the cancers. Bass said these results suggest that inhibitors of the PI3-K pathway could have great utility in these cancers. Furthermore, the findings of elevated levels of PD-L1 and PD-L2, key regulators of the immune response, suggest that emerging immunotherapy agents should be tested in these patients.

• Tumors in which malfunctioning DNA repair mechanisms cause a high rate of mutations—many of them leading to potential activation of cancerrelated signaling proteins that can be targeted with novel precision drugs. About 20 percent of tumors fell into this subtype.

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• The largest category of tumors, making up about half of the cancer specimens, was termed "chromosomally unstable." These contained "a jumble of extra or missing pieces of genes and chromosomes and have a striking number of genomic amplifications of key cancer-promoting genes" for which targeted therapies exist or are in development," Bass said. "This subtype of tumor is frequently found in the junction between the stomach and the esophagus, a type of stomach cancer that has been dramatically increasing in the United States."

• The fourth group was termed "genomically stable" since they lacked the molecular features of the other three types. These tumors, making up 20 percent of the specimens were largely those of a specific class of gastric cancer called diffuse-type tumors, he said. "These tumors are especially deadly because of their ability to metastasize rapidly and because we lack effective therapies." The team identified a novel set of genomic alterations in the RHOA signaling pathway in about 30 percent of these tumors. "This finding opens up an entirely new line of research to allow us to investigate what underlies this deadly form of gastric cancer and to ultimately develop new therapies.' OT

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## **PATIENT PORTALS**

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the use of call centers through which patients are connected to an on-call physician.

At Moffitt, patients tend to use the call center on weekends and evenings rather than using the portal if they need to contact an on-call physician about their care, Hulse said.

## **Making Use Meaningful**

Much of the focus among cancer and other health centers has been on getting a patient portal up and running and not on long-term usefulness, Holland said. "A lot of portals are rudimentary. Patients can access basic health record information and email physicians in a more secure manner, but patient adoption and perceived benefits have lagged."

Patients and their families need education and tutorials for a better understanding of how a portal works and what it can offer, which, in turn, makes the service more valuable, he added.

Physician education is also an important component and encourages provider participation, which can lead to a better doctor-patient relationship, he said. The portal should ultimately improve the level of engagement and enhance communication, not create confusion or worse, anxiety.

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