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Genetic 'fingerprint' shown to predict liver cancer's return

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Scientists have reached a critical milestone in the study of liver cancer that lays the groundwork for predicting the illness's path, whether toward cure or recurrence. By analyzing the tissue in and around liver tumors, an international research team has identified a kind of genetic "fingerprint" that can help predict if patients' cancers will return. The findings appear in the October 15 advance online edition of the *New England Journal of Medicine* and were made possible by a large-scale method for revealing genes' activity, which the researchers show can be applied to tissues that have been chemically preserved instead of frozen. This technical triumph promises to unlock biological information within millions of clinical samples previously intractable to genomic study.

"In most hospitals and clinics, the prevailing method of storing patient tissue involves a chemical fixative, which often precludes future genome-scale analyses. That means the vast majority of patient samples have effectively been off-limits to a variety of important questions," said senior author Todd Golub, who directs the Cancer Program at the Broad Institute of MIT and Harvard and is the Charles A. Dana Investigator in Human Cancer Genetics at the Dana-Farber Cancer Institute. "Our work reveals that it is indeed possible to access this biological trove, a step we hope will bolster future genomic discoveries throughout the scientific community."

Unlike many cancers, hepatocellular carcinoma, a form of liver cancer, is often detected early. That is because in the developed world, doctors can identify and closely monitor individuals at highest risk — those with

a history of liver damage due to infection or chronic alcohol abuse, for example. Yet even with early diagnosis and treatment, the disease often recurs. And that development often proves fatal. The ability to pinpoint in advance those most at risk of suffering recurring cases could improve treatment, perhaps helping doctors choose more aggressive therapies for patients whose disease is most likely to return and identifying patients whose health should be carefully followed.

Genome-scale technologies are a powerful means to help develop such predictors, particularly methods that measure the activity (or "expression") of every human gene. However, a major obstacle to applying such methods to hepatocellular carcinoma, as well as other cancers, has been the technical requirements — samples must be frozen, not preserved, or "fixed," in the chemical formalin.

An international team of researchers from the Broad Institute, Harvard Medical School, Dana-Farber Cancer Institute, Mount Sinai School of Medicine, and elsewhere came together to develop an enhanced method for measuring gene expression in formalin-fixed tissues and applied it to samples from more than 300 liver cancer patients. Their work uncovered a striking pattern — a characteristic signature of more than 180 active and inactive genes linked with increased patient survival. Interestingly, this putative predictor was discovered not within the tumors per se, but within the normal tissue surrounding them.

In the future, the telltale gene signature could help distinguish patients whose tumors are likely to return. "Our findings underscore the potential of genomic signatures to help identify treatments that will be most beneficial to individual patients," said Golub, who is also an investigator at the Howard Hughes Medical Institute.

The discovery flows from an existing gene expression method that works on formalin-fixed tissues yet extracts information on just a few hundred

genes. The researchers redesigned the technique to analyze roughly 6,000 genes — a subset that yields sufficient data to either directly measure or infer the expression levels of nearly all ~20,000 human genes.

Although further work is needed before the liver cancer findings can be used in the clinic, the current study marks a key step toward accelerating genomic discoveries with medical promise. Indeed, most patient tissue banks, especially those with valuable clinical data such as disease severity and course that are so vital to retrospective studies, are built from fixed samples and up until now have been largely inaccessible to genomic analysis. "In the Boston-area hospitals alone, we estimate that there are more than one million archived samples that can be analyzed with this approach," said Golub. "There's a wealth of information waiting to be explored."

Source: Broad Institute of MIT and Harvard