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News

Personalized cancer therapy gets closer

Genetic testing allows doctors to select best treatment.

Erika Check Hayden

Some patients with cancer have gene mutations that can be targeted by specific drugs.BURGER/PHANIE/REX FEATURES

The long-awaited era of personalized genetic medicine may finally be arriving for people with cancer. Some cancer centres are preparing to screen all patients for genetic glitches associated with the disease, and scientists are starting to use detailed information about patients' tumour genomes to decide which treatments might benefit them most. "Oncology is absolutely farther down this road of personalized medicine than other areas," says Joan Scott, deputy director of the Genetics & Public Policy Center in Washington DC.

Treatments that target specific mutant genes have been available for certain cancers since 2001, and a handful of studies have pinpointed mutations that reveal which tumours will respond best. For instance, mutations in the epidermal-growth-factor receptor (EGFR) gene affect how well patients with lung cancer respond to drugs that target the EGFR protein. But recent studies have highlighted the shortcomings of this one-gene-at-a-time approach by showing that the genetic roots of many cancers are both complicated and blurred: a wide variety of rare mutations can cause any one type of cancer[1], and mutations in the same genetic pathways occur in many tumour types.

Last week, the Massachusetts General Hospital in Boston announced that it will carry out broad genetic testing of almost all patients with cancer, screening for 110 mutations in 13 cancer-related genes (see table). Other hospitals are also moving in this direction: the Memorial Sloan-Kettering Cancer Center in New York City, for example, already tests 40 mutations in seven genes in all patients with lung or colorectal cancers. By picking up mutations in key genetic pathways, the tests could help oncologists to choose drugs that have been approved or are in clinical development. "In the next few years, I think every major cancer centre is going to work on this approach," says molecular pathologist John Iafrate of Massachusetts General Hospital.

PATIENT CANCER GENES UNDER SCR

Gene tested (by whom)	Implicated in which major ca
APC (MGH)	Brain, colorectal, liver, sto
Beta-catenin (MGH)	Brain, colorectal, liver, lun
BRAF (MGH, MSKCC)	Colorectal, lung, skin, thy
EGFR (MGH, MSKCC)	Lung
FLT3 (MGH, MSKCC)	Blood
JAK2 (MGH, MSKCC)	Blood
KIT (MGH)	Blood, gastrointestinal, g
KRAS (MGH, MSKCC)	Colorectal, lung, pancrea
NOTCH1 (MGH)	Blood
NRAS (MGH)	Blood, colorectal, thyroid
TP53 (MGH)	Anal, bladder, bone, brain lung, skin, soft tissue
PIK3CA (MGH, MSKCC)	Brain, breast, colorectal,
PTEN (MGH)	Blood, brain, breast, cerv
MEK1 (MSKCC)	Lung
AKT1 (MSKCC)	Breast, colorectal, lung, c
HER2 (MSKCC)	Breast, ovarian

MGH, Massachusetts General Hospital; MSKCC, Memorial Sloan-K

Such advances are possible because the cost of genetic screening and sequencing technologies

has been dropping precipitously. Hospitals can amplify and read out single altered 'letters' — or point mutations — in the DNA sequences of tumour genes commonly implicated in certain cancers. And academic researchers are a step beyond this, using high-speed sequencing to collect information about every gene in individual patients' tumours.

Last month, for example, Marco Marra, director of the British Columbia Cancer Agency's genome sciences centre in Vancouver, told attendees at the Advances in Genome Biology and Technology meeting on Marco Island, Florida, that his group had sequenced the whole genome of a tumour that had spread from one patient's mouth to his lung. The group had also used gene-expression studies to compare the activity of his tumour genes to those in healthy tissue.

They found that the patient had mutations in a tumour-suppressor gene called PTEN, and abnormally high expression of a gene downstream of PTEN, called RET. This explained why he had not responded to treatment with the drug erlotinib, and fits with some earlier studies suggesting that patients with active PTEN respond better to erlotinib[2]. Marra's team recommended instead that the patient be put on a drug called sunitinib, which inhibits the protein made by RET. The patient's cancer subsequently regressed.

"This work illustrates how one can potentially use next-generation sequencing technologies to establish the appropriate course of cancer treatment for individual patients," says Eric Green, scientific director of the National Human Genome Research Institute in Bethesda, Maryland.

Studies such as Marra's are being conducted in many patients to find genetic traits that could predict how tumours respond to treatment. And such studies are likely to increase as the cost of genome sequencing drops. Rick Wilson, director of the Genome Sequencing Center at Washington University in St Louis says that it cost more than $1 million for his centre to sequence the first tumour genome last year[3]. He estimates that the second tumour genome sequenced at the university cost $500,000, and projects that this could drop to $50,000 per tumour by early next year.

Some businesses are finding that a handful of patients — who may already be paying thousands of dollars for their diagnosis and treatment — are willing to pay this sort of money for cancer-related genetic information. Last year, for example, a company called CollabRx, based in Palo Alto, California, began offering a service that analyses 15,000 genes, looking at gene expression, copy number and single-base mutations in individual patients' tumours for between $50,000 and $100,000. Five patients have used the service, which aims to determine which available drugs might be most suitable. Jay Tenenbaum, the company's founder and chairman, calls CollabRx's approach "personalized oncology research" because the results of each patient's individual analysis are used to help guide future analyses in other patients.

But because only a few drugs can currently be selected on the basis of specific mutations, "you have to be careful with raising expectations with that kind of approach", says Marc Ladanyi, chief of molecular diagnostics at the Memorial Sloan-Kettering Cancer Center.

Anna Barker, deputy director of the National Cancer Institute in Bethesda, is optimistic that treatment options won't stay limited for long. Genomic data being gathered from patients with cancer should help researchers to identify the genetic signatures that correlate with different symptoms or rates of disease progression — and hence guide the development of drugs. Barker predicts that these signatures will also be used in the future to help doctors to combine existing drugs to target multiple genetic pathways and attack specific attributes of each patient's cancer. "I'm very optimistic that we can move in this direction, and it should be a more cost-

effective and better way of taking care of cancer patients," she says.

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