Basket trial approach capitalizes on the molecular mechanisms of tumors

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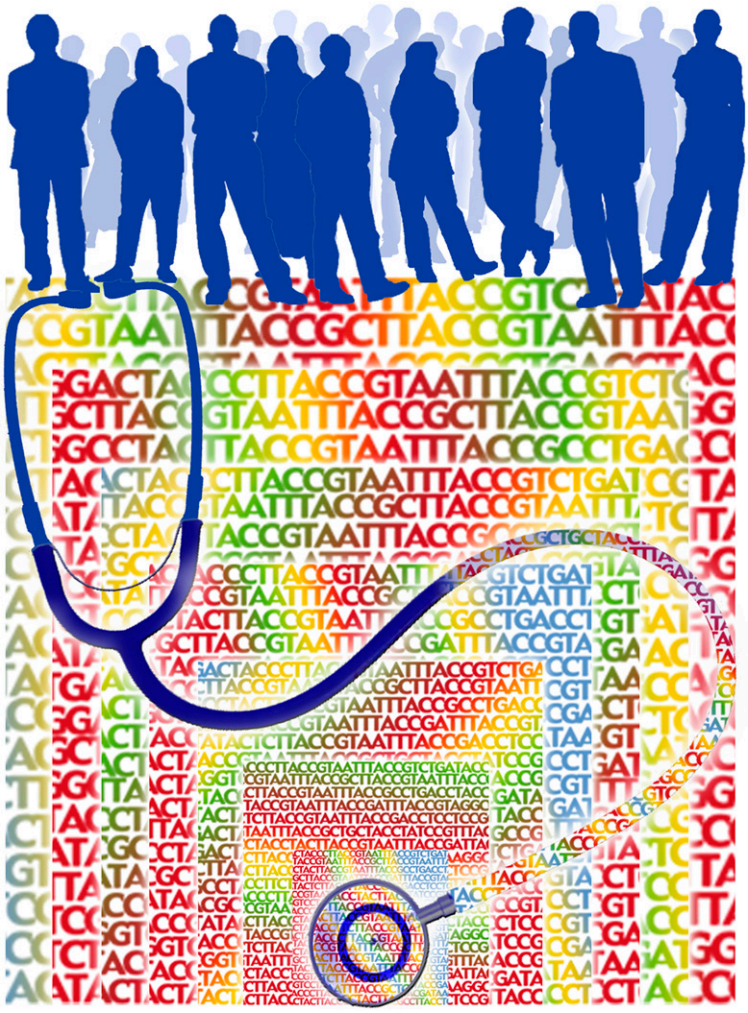
Traditional clinical trials reflect a traditional way of thinking about cancer. Patients diagnosed with cancer in the same tissue or organ receive the same therapy under the assumption that they share the same disease. But under the microscope, no two cancers are actually the same; tumors differ from patient to patient. A few patients may noticeably improve with treatment, whereas most experience no benefit at all [see "Capturing cancer's complexity" in PNAS (1)]. As researchers learn more about cancer's heterogeneity, they're calling for sharper investigational strategies that match a genetic understanding of the disease. One result has been "basket trials," a strategy that groups patients not by tumor site, but by genetic signature, in the hope of better identifying the population most likely to benefit from a drug (2).

Chemotherapy typically targets wide swaths of fast-dividing cells. As early as the late 1980s, researchers began developing drugs to target specific molecular culprits that drive a tumor. One of the first of these drugs was trastuzumab (Herceptin), which increases survival for patients with breast cancer whose tumors overexpress a protein called HER2. Approved in 1998, that drug has saved many lives: about a quarter of all breast cancer patients overexpress HER2. A string of drugs has followed, each targeting particular molecules within the tumor's cells. But testing them has been difficult, as many cancer drugs fail to deliver results in one-size-fits-all studies in people.

In retrospect, that's not surprising, says oncologist Keith Flaherty, who directs the Termeer Center for Targeted Therapies at the Massachusetts General Hospital Cancer Center. "Most early attempts to develop targeted therapies didn't have a clear path for being investigated in a biomarker-defined population," says Flaherty. Those attempts focused on clinical diagnosis and cancer type rather than mutations. It took about a decade, he says, for the field to catch up to the reality that clinicians needed a new strategy.

Group Therapy

In the last five years or so, says Flaherty, researchers at major cancer centers and universities have begun to take a different approach. Instead of traditional phase I trials, which assess a drug's safety, they began to run so-called "phase I/II" trials, which allow for the dose of a targeted drug to be increased in patients who clinicians predicted would respond positively. These sorts of trials helped measure results in a small patient population—such as a subset with a particular mutation—but were often still limited to a single cancer-affected organ or tissue. That phase I/II approach, combined with genetic information about a patient's tumors, evolved into the idea of putting patients into defined groups, called "baskets."



In hopes of zeroing in on patient populations likely to benefit from a given drug, researchers are attempting a strategy that groups patients primarily by genetic signature rather than tumor site. Image courtesy of Jane Ades (National Human Genome Research Institute, Bethesda).

Flaherty says two new technologies made basket trials possible. First, researchers needed a suite of targeted therapies from which to choose. Second, researchers needed a catalog of mutations that were likely drivers of the disease. With those two pieces in place, Flaherty and other researchers could design new clinical trials around that portfolio, matching the patients and the drugs as quickly as possible.

The basket trial is a tool of the age of precision medicine, based on the idea that a targeted drug needs a

targeted trial. In a basket trial, researchers group patients primarily according to genetic mutations that may drive their disease, rather than by disease site or histology. [Thus far, researchers have identified about 140 genes that, when mutated, give the cell a small growth advantage (3).] So-called "truncal mutations" in these genes occur in the original cancerous cell and all of its clones. For the most part, targeted drugs target truncal mutations. Patients then receive an experimental therapy that targets molecules associated with those mutations.

Basket trials do have limitations: Because tumors are so heterogeneous, actionable mutations may be missed in the biopsy, for example. Nevertheless, the hope is to greatly increase the chances of identifying the patient population most likely to benefit from the drug. Last August, in some of the first published results from a basket trial, researchers from Memorial Sloan Kettering Cancer Center in New York City reported that a drug that targets a mutation in melanoma may also be effective in patients with lung cancer (4).

Flaherty, whose work has focused on targeted treatments for melanoma and kidney cancers, says basket trials grew out of a need for more targeted therapies in patient populations that needs them the most. "Once you have 10 or 20 or 30 more investigational agents in the pipeline, it becomes really inefficient to [be] hunting biomarker by biomarker, patient subpopulation by subpopulation, even before you knew if a drug had legs," he says. "Now it makes more sense for patients to enter the pipeline with some broad genetic characterization." Researchers need to figure out which patients are mostly likely to benefit from the drugs the Food and Drug Administration (FDA) has approved, ranging from immunotherapies to gene-expression modulators to monoclonal antibodies.

Flaherty has an idea of how to do that. He says researchers need to develop preclinical models that indicate which drugs will be effective for which cancer type and which targeted populations. Vemurafenib and dabrafenib, for example, both inhibit a protein called BRAF kinase. These drugs were originally shown to be effective in patients with metastatic melanoma; the FDA went on to approve them both. Now researchers are trying to determine if the drugs may also play a role in the treatment of colorectal cancer patients with the same mutation.

Perfect Match?

A large study developed by the National Cancer Institute (NCI) and led by the Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN) Cancer Research Group greatly expands on the idea of a basket trial. The study, called NCI-MATCH (Molecular Analysis for Therapy Choice) opened for enrollment in August 2015 to patients receiving treatment at a facility in the NCI's National Clinical Trials Network or the NCI Community Oncology Research Program.

Patients who enroll in the trial undergo a tumor biopsy and DNA sequencing. If their tumor has a targeted variant that matches one of the treatment groups, clinicians assign the patient a matching experimental therapy. (The NCI doesn't charge for the biopsy and sequencing, and pharmaceutical partners provide the drugs.) Flaherty, a MATCH cochair, and his collaborators designed the study to allow groups to be added in additional arms or dropped as needed. MATCH enrolled 795 patients last summer and fall. Enrollment paused in November during a planned hiatus as researchers authenticated data.

NCI oncologist Alice Chen, also a MATCH coleader, says the trial, which is accessible to cancer centers large and small across the country, is designed to reach a lot of patients, especially those with unusual tumors who may not have many treatment options. "There is a lot of enthusiasm both from investigators and from patients for this type of treatment," she says.

In addition to major cancer centers, the trial has reached out to community oncologists at small hospitals who do not always have access to rare tumor trials or investigational treatment trials. To further bolster the reach of the trial, she says the NCI and ECOG-ACRIN plan to make their data available to other cancer researchers in the near future. MATCH is a discovery trial, an attempt to identify promising new avenues of treatment for certain groups of patients.

James Doroshow, deputy director for clinical and translational research at the NCI, called MATCH "the largest and most rigorous precision oncology trial in history" at a press conference last summer (5). Even so, the organizers have a lot of room to grow. According to the interim results, presented in New Orleans in April at the annual American Association for Cancer Research meeting, only 33 of the 795 enrolled patients were found to have "actionable" mutations and be eligible for assignment to a treatment group. As of the meeting, 16 patients had entered the trial.

And because basket trials will include many different types of patients and many different mutations, determining statistical significance will be a challenge. Although this isn't a priority for the discovery trial, future efforts will have to grapple with how to confirm meaningful outcomes. Chen notes that the MATCH investigators have had to clearly identify how they measure disease progression in each case.

Regardless, there's still a fundamental question left to be resolved: Will matching targeted drugs with genetic variations be more effective than standard care?

In effort to find out, MATCH is scheduled to reopen in late May with 14 additional arms, which will allow the researchers to test an even wider swath of patients and drugs. "Our intent is to provide leads so that, in a very broad fashion, we hasten drug development in many areas," Chen says. "The timing is perfect for this right now."

1 Williams SCP (2015) News feature: Capturing cancer's complexity. *Proc Natl Acad Sci USA* 112(15):4509–4511.
2 Redig AJ, Jänne PA (2015) Basket trials and the evolution of clinical trial design in an era of genomic medicine. *J Clin Oncol* 33(9):975–977.
3 Vogelstein B, et al. (2013) Cancer genome landscapes. *Science* 339(6127):1546–1558.
4 Hyman DM, et al. (2015) Vemurafenib in multiple nonmelanoma cancers with BRAF V600 Mutations. *N Engl J Med* 373(8):726–736.
5 Andrews A (2015) ASCO and NCI launch largest precision medicine trials using real-world evidence. *American Health & Drug Benefits* 8(Spec Issue):37.