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Medical News & Perspectives

# A Precision Medicine Approach to Clinical Trials

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Five or 6 years ago, only 5% to 10% of patients at David Hong, MD's clinic arrived with a mutational profile of their tumor. Today, it's more like 25% to 30%. They come bearing their tumor profile in the hope that they'll qualify for one of a growing number of clinical trials targeting specific biomarkers, a strategy called precision medicine. Desperate, some come already knowing that they qualify for a particular trial, thanks to Facebook groups for cancer patients whose tumors share the same genetic abnormality and other online resources.

"They say, 'Dr Hong, I want to be in this trial,'" said Hong, deputy chair of the department of investigational cancer therapeutics at the University of Texas MD Anderson Cancer Center. "Patients are incredibly savvy. Especially if they have end-stage cancer and their doctor has told them, 'there's nothing more I can do for you,' they will find a trial."

Scientists as well as patients pin much hope on clinical trials that use a precision medicine approach, one in which biomarkers, not simply diagnoses, guide enrollment. In its report presented on September 7 to the National Cancer Advisory Board, the blue ribbon panel for the national "Cancer Moonshot" initiative called for a large-scale network through which patients would be offered tumor profiling and information about treatments and clinical trials that might be appropriate given their tumor profile.

Such trials hold the promise of faster drug development as well as a potentially bigger therapeutic payoff for participants than do conventional randomized controlled trials. Besides enrollment criteria, precision medicine trials also differ from tradi-

tional RCTs in their design, which might include far fewer participants, and may not include a placebo or standard care comparison group.

But trials of targeted treatments also have their limits. Hong and other researchers note that even in the cancer field, most patients lack a target against which available biomarker-based therapies could take aim. And even those with an "actionable" tumor—one containing a mutation that could be treated with a targeted therapy—might not be cured, because their tumor contains other genetic abnormalities.

Despite those potential obstacles, enthusiasm isn't in short supply. "There are cases where the precision medicine paradigm is honestly clearly going to work," said David Goldstein, PhD, director of Columbia University's Institute for

Genomic Medicine, part of the school's Precision Medicine Initiative.

Evolutionary, Not Revolutionary

While President Obama launched the Precision Medicine Initiative only a year-and-a-half ago, the concept—"delivering the right treatment at the right time, every time, to the right person," as Obama described it—is as old as medicine itself, noted US Food and Drug Administration (FDA) Commissioner Robert Califf, MD, a cardiologist and clinical trials expert.

"The reason this is so hot right now is that all the technologies and science have come together to accelerate what's already being done," Califf said. "I don't tend to see this as revolutionary, but more evolutionary." For example, the investment in the Human Genome Project, completed in



## Precision Medicine Trials in Oncology

**Master Protocol:** Enrolls patients with a certain type of cancer. Patients are screened for various biomarkers, and assigned to 1 of several sub-studies—basket or umbrella trials—of targeted treatments most likely to be effective for a given biomarker profile. The master protocol guides implementation of all sub-studies of biomarker-drug combinations, and may include a “non-match” arm where patients without a known biomarker are assigned to treatment, placebo, or standard care.

**Basket Trial:** Enrolls patients based on the specific genetic abnormalities in their tumors, regardless of where their tumor originated in the body. The trial is governed under a “master protocol.”

An example includes the NCI-MATCH trial.

- **NCI-MATCH:** As many as 5000 patients with solid tumors or tumors that don't respond to medication will be screened for mutations in 143 genes. Patients will then be assigned to a specific treatment arm for a targeted drug that matches their tumor's genetic profile.

**Umbrella Trial:** Enrolls patients with the same type of cancer but assigns them to treatment with 1 of several different

targeted therapies. The trial is governed under a master protocol. Examples include 2 NCI lung cancer trials, Lung-MAP and ALMECHIST.

- **Lung-MAP:** Between 500 and 1000 patients with advanced squamous cell lung cancer will have their tumors screened for genetic mutations. Each patient will be assigned to a treatment arm according to their tumor's genetic profile.
- **ALCHEMIST:** From 6000 to 8000 patients with early-stage non-small cell lung cancer will have their tumors screened for mutations in *ALK* or *EGFR* genes. Patients will be assigned to a treatment arm to receive an *ALK* or *EGFR* inhibitor depending on their tumor's genetic profile.

**N of 1:** Enrolls individual patients with a previously determined genetic tumor profile. Each patient is randomly assigned to placebo or a different sequence of anticancer compounds matched to their tumor genotype, with washout periods in between. Patients serve as their own control group in determining treatment efficacy. Alternatively, investigational drugs may be tested on individual patient tumor samples *in vitro* or in animal models.

2003, now “is playing out beautifully in oncology,” he said.

The FDA already has approved many treatments based on precision medicine trials, Califf noted. Some have been approved after trials in only a couple of hundred patients—fewer than conventional phase 3 randomized controlled trials, which might enroll up to 3000 patients. Of course, the potential market for some targeted therapies isn't as large as the size of some phase 3 trials.

“We don't think of clinical trials as necessarily small or large,” Califf said. “The trial should be sized to produce the power needed to detect the expected effect of the treatment. If the effect is large, the trial can be small. If the effect is modest and the population is large, it is still worthwhile, but a larger trial is needed.”

His own 88-year-old mother, diagnosed with multiple myeloma 8 years ago, is taking daratumumab, a targeted therapy that was tested in fewer than 200 patients before the FDA approved it in November 2015, Califf said. “If you have a situation like hers, where she's already failed multiple therapies...that's where the

exceptions are being made,” as far as the size of the trial and whether it requires a control group. In the 2 [safety and efficacy trials for daratumumab](#), all 148 patients enrolled received the drug.

In cases where a tumor mutation is very rare, testing the efficacy of investigational treatments with the traditional clinical trial design is nearly impossible. So researchers have proposed so-called N-of-1 precision medicine trials, which aim to study targeted treatments for tumors in individual patients. For example, Columbia University Medical Center researchers, led by Andrea Califano, PhD, chair of the systems biology department, is enrolling 260 patients with any one of 13 rare or untreatable cancers into a round of N-of-1 trials. Participants' tumor tissue will undergo DNA sequencing and RNA expression analysis in the search for genes that are “master regulators” of cancer maintenance and progression. The scientists then look for drugs that are FDA-approved or in advanced clinical trials that target the master regulator genes in each tumor. Relevant drugs are tested on the tumor sample, either in cell culture or after implantation in a mouse. If the drug stops

tumor growth, it might be tested in a conventional clinical trial.

While this particular round of N-of-1 trials isn't designed to provide treatments to participants, if a drug is found to shrink a tumor, that information might be shared with the patient's physician. “We always make an effort and generally succeed in getting [treatment outcome] information to the treating oncologist when something relevant emerges,” Califano noted.

Most of the more than 20 cancer drugs that received FDA approval last year were targeted therapies, and many were expedited through a combination of regulatory pathways, such as the orphan drug or breakthrough designations, Califf explained.

In a [recently published analysis](#) of 63 anti-cancer drugs that received FDA approval between August 1998 and July 2014, the 28 precision medicine therapies studied had shorter clinical development periods—on average 58.8 months compared with 93.5 months for the 35 non-targeted drugs in the analysis—but took about as long to go from New Drug Application submission to approval.

Another study, of cancer treatments approved by the FDA from September 1998 to June 2013, found that a biomarker-based approach to clinical trials of anti-cancer drugs was associated with improved efficacy and longer progression-free survival relative to conventional trials.

### MATCH Points

More evidence that patients are clamoring to participate in clinical trials taking a precision medicine approach comes from the National Cancer Institute's (NCI) Molecular Analysis for Therapy Choice (NCI-MATCH) Trial, which is analyzing patients' fresh tumor biopsies to see whether they contain genetic abnormalities for which a targeted drug appears promising.

It's highly likely that patients whose tumors originated in different parts of the body could have the same abnormality, said Nita Seibel, MD, head of Pediatric Solid Tumor Therapeutics in the Clinical Investigations Branch of the NCI's Cancer Therapy Evaluation Program. “We don't care where it originated. All we care about for treatment selection is the genetic abnormality.” In August 2015, NCI-MATCH began enrolling patients aged 18 years or older into 10 treatment arms.

Investigators expected it would take a year to screen 500 patients' tumors, at which point the study would pause to conduct an interim analysis. But NCI-MATCH ended up screening 795 patients—it couldn't stop at 500 because so many were already in the screening pipeline—before temporarily halting enrollment in November, less than 4 months after it began. The trial resumed in May with 24 treatment arms that will enroll up to 35 patients each.

"The response was unbelievable," Seibel said. Standard therapy had failed to cure the patients, she said, so "they're very interested in anything they could get, particularly if it could be developed specifically to target their tumor."

Most of the arms are testing a single experimental drug that appears to target a single genetic abnormality or a group of related genetic abnormalities, she said. A few arms are testing combinations of 2 drugs. Many different companies have given NCI-MATCH the go-ahead to test their drugs, Seibel said. As long as their tumor doesn't grow, patients can continue taking the drug, Seibel said. "If their tumor starts to grow, they would come off the drug." At that point, it is recommended that they get another biopsy to see if they are eligible for any other arms, she said. If a patient's initial biopsy didn't match a treatment but a treatment is added later that might be a match, the patient's physician will be notified.

Originally, NCI-MATCH had expected that 30% of patients screened would be candidates for an arm of the trial, but so far only 10% have been, Seibel said. "The reality of the situation is that the percentage of patients whose tumor will have a genetic abnormality that could be targeted with a drug is low." When NCI-MATCH expands to 30 arms this fall, Seibel said, she anticipates that perhaps 20% to 30% of screened patients will have clinically actionable tumor mutations.

### Beyond Cancer

Precision medicine clinical trials in cancer are setting the stage for tackling other diseases.

With neurological conditions, Goldstein said, "we have fundamentally a simpler problem than cancer as long as we can figure out what the mutation does in order to cause disease." Targeting a treatment to undo or compensate for what the mutation does can represent a cure, he said.

Sometimes, though, scientists struggle to figure out the role of mutations, Goldstein noted. For example, he said, while his laboratory and others have identified many genetic variants associated with amyotrophic lateral sclerosis (ALS), they don't know how the mutations actually might cause the disease.

Epilepsy has been a major focus of Goldstein's research. Mutations in the *KCNT1* gene have been implicated in several drug-resistant epilepsy syndromes. "These are

often very, very sick children" who represent a "miniscule" proportion of epilepsy cases, he said.

The *KCNT1* gene provides instructions for making potassium channels, which transport potassium in and out of neurons and play a key role in their ability to generate and transmit electrical signals. *KCNT1* mutations in epilepsy cause potassium channels to generate too much current, Goldstein said.

He and colleagues in Melbourne, Australia, [recently reported](#) on the use of quinidine, a *KCNT1* inhibitor, to treat 2 children with drug-resistant epilepsy who had mutations in the gene. One child had an 80% reduction in seizure frequency; the other did not improve.

The Australian researchers have conducted a small formal trial of quinidine in young epilepsy patients with *KCNT1* mutations but have not yet published their findings, Goldstein said. The problem with quinidine is that it can cause cardiac toxicity when given in the large doses needed to inhibit *KCNT1*, he said.

"We have to be very realistic and sober about how long this is all going to take," Goldstein said of precision medicine trials. "A very, very large number of very small steps—that's the way it's going to work. It's going to be a wonderful contribution to medicine, I have no doubt, but it's going to take a lot of time and a lot of effort." ■

**Note:** The print version excludes source references. Please go online to [jama.com](http://jama.com).