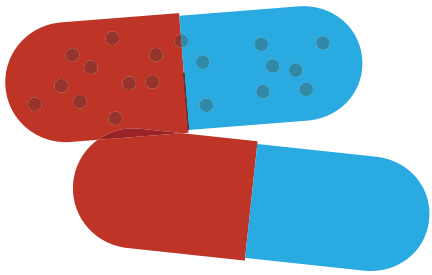


Outsmarting the placebo effect

Can a genetic test to predict a person's level of placebo response help new drugs win approval?

By **Kelly Servick**

Kathryn Hall's early career was built on pharmaceuticals, not placebos. A molecular biologist, she had spent 2 years identifying drug targets at Millennium Pharmaceuticals, when in 2005, she found herself in an acupuncturist's office seeking any possible relief from persistent carpal tunnel syndrome in her wrists and hands. "I remember sitting there thinking, I can't believe I'm doing this. This is so ridiculous," she says.

As the first needle slid in, Hall felt a "god-awful" shooting sensation, and she hasn't had carpal tunnel problems since. The needles might have had a physiological effect, Hall acknowledges. Yet she also became fascinated by the possibility that her relief was partially due to the placebo effect: genuine benefit that patients derive from the mere expectation of treatment.

Years later, Hall is a researcher in the Program in Placebo Studies and the Therapeutic Encounter at Harvard Medical School's Beth Israel Deaconess Medical Center (BIDMC) in Boston. And her first published work on the subject, describing a gene that in a small study correlated with a person's degree of placebo response, has become the basis of an unusual company called Biometheus. The firm's CEO, Gunther Winkler, hopes to offer drug developers a tool that predicts and controls for the placebo effect in clinical trials, where a strong response to a sugar pill can muddy the data and derail the approval process.

Drug developers have longed for a way to control for the placebo effect. So the prospect of a predictive test is "certainly intriguing and worth investigating," says Amir Kalali, a neuroscientist and drug development expert at the large contract research organization Quintiles in San Diego, California. Kalali was among those attending a session at the Biotechnology Industry Organization's annual meeting in June in San Diego, where Winkler and Hall presented the new company's premise. Yet some veterans of research on the mysterious, complex placebo effect are cautious. "It feels a little premature at this point in time to think that one single gene will give us predictive value in clinical trials," says Jon-Kar Zubieta, a psychiatrist and neuroscientist at the University of Michigan, Ann Arbor.

THE PLACEBO EFFECT can be a gift to people suffering from a variety of conditions, but it's a bedeviling problem for drug companies. "Drug discovery is not about whether a drug works," says Ted Kaptchuk, who directs the Harvard placebo lab. "It's about whether it works better than a placebo control." For conditions where placebo groups tend to show huge improvements in clinical trials—especially pain, depression, and other psychiatric disorders—outperforming a fake treatment is a real hurdle. One study found that only 53% of acute depression trials submitted to the U.S. Food and Drug Administration (FDA) between 1983 and 2008 showed the antidepressant under review beating the placebo.

Winkler wrestled with unpredictable placebo responses during his 23 years developing drugs and running clinical trials for Biogen Idec. While preparing to test a treatment for psoriasis, a poorly understood condition that often causes skin irritation and joint pain, he researched previous trials of potential treatments and found placebo response rates from 5% to 30%. "Where do you start?" he wondered. "Assume 5%, run a small trial, and fail? Or start with the assumption of 30%, and have a very big trial which costs a lot of money and may preclude the drug developer from running other studies?"

Some people may show a placebo response simply because they signed up for a trial at a low point in their illness and then

naturally get better. But some fraction may experience a genuine placebo effect—which appears to be stronger for some individuals than others. Personality tests have linked a strong response to traits such as "agreeableness," "ego-resilience" and "novelty-seeking," but these associations have been hard to generalize across disease groups or studies. So have reported links between responsiveness to placebo and distinctive features seen in brain imaging.

Hall joined the Harvard lab hoping to identify genetic factors in the placebo response. She was quickly enticed by a gene that encodes the enzyme catechol-O-methyltransferase (COMT), which breaks down catecholamines—a family of compounds that includes the neurotransmitters dopamine and epinephrine. In pain studies done by other labs, people who inherited two copies of the "val" form of the gene reported feeling less pain than those with two of the "met" form. If the met-met types sense pain more acutely, Hall thought they might also be more sensitive to the pain relief of the placebo effect.

Hall's logic was straightforward: Placebo response has been linked to release of dopamine, a major player in the brain's reward system, in the prefrontal cortex, and the met form of *COMT* is three to four times slower to break down dopamine than the val form of the enzyme is. As a result, Hall suspected, the met form allows dopamine to linger, creating a more intense feeling of pain relief after treatment—whether it's drug or placebo.

In the first group of patients she observed, Hall found a tidy correlation: People with irritable bowel syndrome (IBS) seemed to fall along genetic lines in their response to a sham acupuncture treatment (where needles only appeared to penetrate the skin). Overall, the sham acupuncture recipients reported significant improvements compared with those who got no treatment. But met-met types had especially large gains—on average, 50 points higher than val-vals on a 500-point scale of severity. Patients with one of each allele fell in between, Hall reported in *PLOS ONE* in 2012.

Hall is quick to point out that *COMT* influences many neural pathways, so its relationship to placebo is probably much more complicated than dopamine breakdown. "What it's actually doing to which molecules when, that's the mystery," she says.

Because Hall's IBS study relied on self-reported pain, other researchers caution that it can't distinguish between a real improvement in symptoms and so-called response bias—a patient's tendency to report improvements on a questionnaire. In other words, met-met subjects might just be more likely to say they feel better.

Nor is Hall's gene likely to be the full story. In 2008, psychologist Tomas Furmark of Uppsala University in Sweden and colleagues reported that a variant of a gene involved in regulating serotonin production predicted which people with social anxiety disorder symptoms responded most strongly to a sugar pill. Yet for this disorder, Furmark has found no link between *COMT* and placebo response. In 2013, a group led by Zubieta found a gene associated with placebo-induced relief from a painful stimulus among healthy controls, but he doesn't expect the same mechanisms to be at play in lots of other settings.

Helen Mayberg, a neurologist who studies depression at Emory University in Atlanta, sees Hall's *COMT* research as a small piece of what should be a much larger search for biomarkers to gauge both placebo and drug responses. "We are working a la carte," she says, "and this is going to need to be a buffet."

Yet Hall's finding caught the eye of Winkler, a member of BIDMC's board of trustees. If companies could identify and exclude strong placebo responders (met-met types make up roughly 25% of the population, he says), they could create smaller, more statistically powerful trials. Winkler and BIDMC filed for a patent on the concept of screening and excluding potential trial participants based on the *COMT* gene, and another on using the gene to predict placebo responders in the clinic. Hall now serves as an unpaid scientific adviser to Biometheus and would get some modest royalties if it successfully markets a test.

Winkler says several companies researching pain, central nervous system diseases, and autoimmune conditions have expressed interest in the test. He hopes to use large genetic data sets from their completed trials to look for links between *COMT* variants and placebo response in other diseases.

There's reason to think that FDA would support companies using *COMT* to screen trial participants, Winkler says. The agency already endorses a variety of so-called enrichment strategies, which aim to reduce response in the placebo group through crafty trial design. The most common strategy is to give all potential participants a placebo, and then "drop them out if they get too much better," says Robert Temple, deputy center director for clinical science at FDA's Center for Drug Evaluation and Research in Silver Spring, Maryland. But better ways to minimize response in placebo groups "are on everybody's mind."

Yet using the *COMT* gene to select trial participants could raise new complications. For one, it relies on the assumption that strong placebo responders will not also be exceptional drug responders, says Luana Colloca, a clinical neuroscientist with the National Institutes of Health's National Center for Complementary and Alternative Medicine in Bethesda, Maryland. If placebo response and drug response share common mechanisms, eliminating people most susceptible to placebos may also obscure the actual effects of the drug.

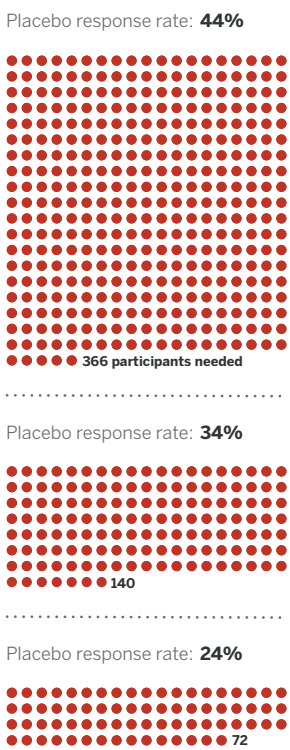
Kevin Weinfurt, a psychologist at the Duke University Clinical Research Institute's program for empirical bioethics in Durham, North Carolina, raises another problem: "You've created a population that doesn't look like the population that's going to receive the drug," he says, "so you're getting the wrong picture of how it will actually work out in practice."

The question is at the front of Winkler's mind, he says, and it came up in a recent meeting with FDA. He says regulators were enthusiastic about using such an approach in early-phase clinical testing, to cut down the cost of finding out if a drug is worth pursuing further. Kalali of Quintiles says that makes the most sense to him, too. "What you really want is the least amount of people possible at the early stages to get the scientific answer that you need."

Meanwhile, Hall has turned to research on how variants of *COMT* influence cardiovascular health and disease. She still "enjoys" acupuncture, but although she's curious which version of the *COMT* gene she has, she decided not to find out. In future studies of the placebo response, Hall says, not knowing her own type may help her stay objective. ■

How to shrink a drug trial

Fewer subjects (●) are needed to see a drug effect when fewer people improve on placebo. Assuming **59%** improve on actual drug:



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