Debate over controlled drug trials escalates

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Growing up in California's rural Central Valley, the two cousins spent summers racing dirt bikes and Christmases at their grandmother's on the coast. They bought each other matching hard hats and sought iron-working jobs together. They shared a love for the rush that comes with hanging steel at dizzying heights and a knack for collecting speeding tickets.

And when, last year, each learned that a lethal skin cancer called melanoma was spreading rapidly through his body, the men found themselves with the shared chance of benefiting from a recent medical breakthrough.

Months before, a new drug had shown it could safely slow the cancer's progress in certain patients. Both cousins had the type of tumor almost sure to respond to it. And major cancer centers, including the University of California, Los Angeles, were enrolling patients for the last, crucial test that regulators required to consider approving it for sale.

"Dude, you have to get on these superpills," Thomas McLaughlin, then 24, whose melanoma was diagnosed first, urged his cousin, Brandon Ryan. McLaughlin's tumors had stopped growing after two months of taking the pills.

But when Ryan, 22, was admitted to the trial in May, he was assigned by a computer lottery to what is known as the control arm. Instead of the pills, he was to get infusions of the chemotherapy drug that has been the notoriously ineffective recourse in treating melanoma for 30 years.

Even if it became clear that the chemotherapy could not hold back the tumors advancing into his lungs, liver and, most painfully, his spine, he would not be allowed to switch, lest it muddy the trial's results.

"I'm very sorry," Dr. Bartosz Chmielowski, the UCLA oncologist treating both cousins, told Ryan's mother, Jan. He sounded so miserable that afternoon that Jan Ryan, distraught, remembers pausing to feel sorry for the doctor.

Controlled trials have for decades been considered essential for proving a drug's value before it can go to market. But the continuing trial of the melanoma drug, PLX4032, has ignited an anguished debate among oncologists about whether a controlled trial that measures a drug's impact on extending life is the best method for evaluating hundreds of genetically targeted cancer drugs being developed.

Defenders of controlled trials say they are crucial in determining whether a drug extends life more than competing treatments.

"I think we have to prove it," said Dr. Paul Chapman, an oncologist at Memorial Sloan-Kettering Cancer Center who is leading the trial. "I think we have to show that we're actually helping people in the long run."

Critics of the trials argue that the new science behind the drugs has eclipsed the old rules -- and ethics -- of testing them. They say that in some cases, drugs under development, PLX4032 among them, may be so much more effective than their predecessors that putting half the potential beneficiaries into a control group, and delaying access to the drug to thousands of other patients, causes needless suffering.

The Lazarus effect

The debate over the controlled testing of PLX4032 began in June 2009, around the time McLaughlin felt something under his right armpit.

The drug, manufactured by Swiss pharmaceutical company Roche, was designed for melanoma patients whose tumors carry a particular mutation, and the company reported that month that nearly all 32 such patients in the drug's first clinical trial, Phase One, had seen their tumors shrink.

The reprieve was brief: Most saw their tumors begin to grow again within the year. Still, The New England Journal of Medicine called the drug "a major breakthrough" for people with advanced melanoma. A second, or Phase Two, trial, aiming to validate the results in more patients, was in the works.

In meetings, several oncologists urged Roche to seek accelerated approval from the Food and Drug Administration (FDA). The agency allows a manufacturer to sell a drug based on early promise so long as it proceeds with the traditional controlled trial comparing it with the standard treatment.

But with patients already begging doctors for the drug, it seemed unlikely anyone would join a trial with only a 50-50 chance of getting PLX4032 once it was already on the market. Unless the trial was conducted before approval, it seemed, there would be no chance to get definitive data on its effectiveness.

Some melanoma specialists familiar with the drug would have traded the data for faster access to the drug.

"I know all that I need to know based on the results we already have," said Dr. Keith Flaherty of Massachusetts General Hospital, who led the early clinical testing. "My use of this drug is not going to be informed by testing it against a drug we all hate and would rather never give a dose of again in our lives."

The standard chemotherapy used in melanoma, dacarbazine, slowed tumor growth in 15 percent of patients for an average of two months. By contrast, PLX4032 had halted tumor growth in 81 percent of patients for an average of eight.

Chapman of Sloan-Kettering came up with a new tack: an unconventional bid to speed the drug's approval, rooted in the observation that patients weeks or days from death could get out of bed and off oxygen when given PLX4032, sometimes for months. The doctors working with the drug referred to this as the Lazarus effect; it was unheard of with dacarbazine.

A trial that cataloged PLX4032's effect on the well-being of the sickest patients, Chapman argued, would probably yield fast, tangible results.

Company officials feared that might lead to approval for only a narrow group of the sickest patients. The surest way to get the FDA's endorsement for a broader market was a controlled trial. And with its competitors rushing to get similar drugs to market, the findings of such a trial might give Roche an advantage in marketing its version.

On Sept. 1 last year, the company submitted its plan to the FDA for the traditional, randomized, controlled trial of PLX4032.

The next week was when Ryan, who was working in Colorado, learned his cousin had a health

problem.

McLaughlin, who had no health insurance, had finally visited a doctor about the pain under his arm. It was melanoma, and he would need surgery to remove some lymph nodes.

Cousins' struggles
McLaughlin's surgery, it seemed, had come too late. In the weeks following, small tumors popped up across his body.

When Ryan discovered a swollen node under his own right armpit in October, his mother was not taking any chances. She begged him to go to the emergency room in Colorado. Even so, when the verdict was melanoma, both families were shocked.

Was it genes? Environment? There was no way to know.

Last Thanksgiving, McLaughlin greeted Ryan with the usual bear hug. "Looks like we're doing this together," he said. They left it at that.

Yet both cousins, like the other relatives, believed then that Ryan stood a far better chance of surviving than his cousin. His cancer was rated Stage 3, with no evidence yet that it had spread to distant parts of his body. McLaughlin, at Stage 4, had a tumor ominously near his liver. And Ryan had health insurance, while McLaughlin had none.

It was the mutated gene that the UCLA doctor found in McLaughlin's cancer cells in December that turned his luck around. Called B-RAF, it goes awry in half of the 68,000 Americans who develop melanoma each year, for reasons not well understood, signaling cells to grow uncontrollably.

The mutation meant that he would be eligible for PLX4032's new trial, so the cost of the drug and doctors' visits would be paid by Roche. And it turned out he would get the pills even before the controlled study began, on a small test of the drug's interaction with common drugs such as caffeine and cough syrup.

Because the slots in the trial were reserved for patients with the most advanced cancer, Ryan was not eligible -- yet. Because he had few symptoms, it hardly seemed to matter. After surgery to remove his cancerous lymph nodes and radiation, he was preparing to return to work.

A week after Christmas, McLaughlin took his first pills. But as the tumor on McLaughlin's collarbone began to melt away, a faint spot on Ryan's lung began to grow.

Life-or-death debate
The discontent among some oncologists over the design of the PLX4032 trial spilled over at a scientific meeting sponsored by the Melanoma Research Alliance in late February.

The ethical review boards at dozens of prestigious cancer-research institutions had signed off on the trial, and the leading melanoma oncologists had embraced it: After all, it was the only way to get the most promising drug available for their patients.

But with the trial under way, a few attending the Las Vegas meeting had already had to tell patients they had been assigned to the trial's chemotherapy-control group. And some had begun to question whether an ethical code that calls for doctors to be genuinely uncertain about which of a trial's treatments will be more effective had been breached when it came to PLX4032 versus dacarbazine.

After Chapman presented the recent data from the drug's promising first trial to a packed room, Neal Rosen, a friend and Sloan-Kettering colleague, stood up.

"Excuse me," Rosen said with unusual formality. "But if it was your life on the line, Doctor, would you take dacarbazine?"

The room was silent. "My goal," Chapman shot back, "is to find out as quickly as possible in as few patients as possible whether this works. If we never know, then we're never going to be able to build on anything."

In April, McLaughlin donned a bandanna, a sun hat, a long-sleeved shirt and pants and went to a job building fences on a nearby ranch.

Ryan's health, by contrast, was declining. He returned from work only to sleep. Often, when his mother called, he was too tired to come to the phone. "Sleeping, Mom," he would text her. Or "You have no idea what this feels like, Mom." Or just, "I hurt."

A bitter blow

On May 12, Ryan and his mother drove to UCLA. The cancer had spread throughout his body. Yet that weekend, the family was filled with hope. Chmielowski had found the same gene mutation that McLaughlin had in one of Ryan's tumors. He was eligible for the trial.

But the computer made its assignment the following Tuesday, making sure he would not be getting his cousin's "superpills."

Ryan's mother picked up the call while her son was undergoing radiation for the tumor on his spine. He was on oxygen. "I'm sorry," Chmielowski repeated.

There must be someone higher up to whom she could talk, she said. There was not, he told her. It was completely random. No one could change it.

"Who else has this drug?" Jan Ryan demanded. "We will go wherever we have to go." There was nowhere to go, the doctor explained.

He told Jan Ryan, that if the chemotherapy could stabilize her son for just a month or so, there were two new trials opening that might help him.

Ryan started his infusion the next day. But a week later, he was hospitalized, unable to breathe on his own and in horrible pain.

"Bud brownies," McLaughlin prescribed when he arrived to visit, having already signed himself up for medical-marijuana use. "You get out of here, and I'll make them for you."

Two weeks later, at his cousin's funeral in mid-June, McLaughlin placed Ryan's hard hat in his coffin and helped carry it to the grave.

McLaughlin has now been taking PLX4032 for nine months. He is awaiting his next CT scan.