Ready Player One: Beating Cancer With Game Theory

By **CLIFTON LEAF** August 10, 2018

Imagine the human body as if it were a three-dimensional playing board, its "squares" (or cubes, rather) so tiny as to be invisible to the naked eye—a couple of hundred, or perhaps a few thousand, cubic micrometers in size. Such are the dimensions of most human cells.

Now imagine a brutal game is being played out on this 3D board. Player One is cancer. It makes the first move. And it takes over more and more squares until Player Two—the body's own immune system—recognizes the threat and starts fighting back. Soon, though, the malignant side evades the defenders and gains ground anew. The cancerous tumor gets bigger until, eventually, it takes up so much of the playing board that you (the host of this unfortunate game) can't help but notice and go nervously to the doctor.

That's the first game: cancer stealthily emerging in the body.

But now begins a second one. And here, in theory, the rules change: Player One, this time, is the oncologist—and she or he often begins the game by attacking the cancer with massive doses of cytotoxic drugs. The aim, in this case, is to wipe out Player Two before it can recover and start spreading again.

Sometimes, this straightforward bludgeon of a strategy works. But often—too often, unfortunately—it doesn't. Malignant cells that are resistant to the initial therapy survive and then repopulate; before long, these battle-hardened rebels spread to distant parts of the body. That's called metastasis, and once the process starts, it's very hard to stop. Player Two wins.

This year, the American Cancer Society estimates that this rotten scenario will play out 609,640 times in the United States alone.

But what if you could change the game? That, indeed, is the proposition of a remarkable paper, entitled "Optimizing Cancer Treatment Using Game Theory," which was published in the journal *JAMA Oncology* yesterday. The review article, by Kateřina Staňková of Maastricht University in the Netherlands, and Joel S. Brown, William S. Dalton, and Robert A. Gatenby at the Moffitt Cancer Center in Tampa, Florida, makes a well-argued case for upending the way we treat most cancers today. Rather than try to wipe the disease out in the first move, say the researchers, we ought to force these fast-evolving cells to reveal their treatment escape routes ahead of time—and then systematically block each one.

The "game" of cancer treatment (as opposed to cancer development itself) has two inherent asymmetries, the authors contend: The first is that there's only one "rational" player—the oncologist. Cancer cells don't think or anticipate or plan out a strategy ahead of time; they adapt. The second is that, in this game, the doctor makes the first move. He or she delivers some sort of therapy to the patient and then the cancer cells respond to it—either by dying or evolving (developing resistance to the treatment). Here, the physician is the leader and the cancer is the follower; or to frame it another way, it's a competition between predator (the physician) and prey (the cancer).

But too often, as noted above, the oncologist surrenders both of these advantages by giving a single high-dose therapy or drug regimen for a set period of time, switching therapies only *after* the tumors begin to grow again:

"By repeatedly administering the same drug(s) until disease progression," Gatenby and colleagues explain, "the physician 'plays' a fixed strategy even as the opposing cancer cells continuously evolve successful adaptive responses. Furthermore, by changing treatment only when the tumor progresses, the physician cedes leadership to the cancer cells and treatment failure becomes nearly inevitable."

The cancer, in other words, becomes the leader and the doctor becomes the follower.

Or think of cancer therapy as a game of "rock-paper-scissors"—yes, this is their analogy, not mine.

"If almost all cells within the cancer play, for example, 'paper,' [it] is clearly advantageous for the treating physician to play 'scissors.' Yet, if the physician *only* plays 'scissors,' the cancer cells can evolve to the unbeatable resistance strategy of 'rock.'"

This traditional approach might yield a short-term success (tumor shrinkage or even a full temporary remission), "but failure to anticipate the longer-term evolutionary arc permits the tumor to evolve resistance unopposed," the researchers write.

So what's the solution? One answer might be to try to "steer the cancer" through what they call "therapy probes"—administering smaller doses of different drugs over shorter periods of time to tease out the cancer cells' various responses. (What resistance mechanisms do they evolve, for instance, when given X or Y drug?) The next step is to use this information to target each one of the surviving subpopulations—again, with therapeutic scalpels, not sledgehammers.

The strategy would have been nearly impossible to pull off a generation ago. But the modern tools of precision medicine—which make it much easier to identify populations of cancer cells by their molecular signatures—have made the approach viable.

Gatenby, a mathematical oncologist and the study's corresponding author, has been studying the evolutionary dynamics of cancer for many years and is an acknowledged leader in the field. He and his colleagues also seem to have no shortage of analogies at the ready:

"Consider an eager dog that chases a squirrel by running directly at it," they write. "Coyotes, in contrast, have learned that squirrels respond to pursuit by running toward the nearest tree and, therefore, do the same. In the former contest, the squirrel becomes the leader as the dog follows it in a wide arc toward and up the tree. In the latter, the coyote leads and prevents the squirrel from executing its evasive strategy."

In short, if you want to beat the squirrel, you've got to out-squirrel the squirrel.