Future prostate cancer treatments might be guided by math

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Scientists have designed a first draft of a mathematical model that someday could guide treatment decisions for advanced prostate cancer, in part by helping doctors predict how individual patients will respond to therapy based on the biology of their tumors.

These decisions would apply to treatment of cancer that has already spread beyond the prostate gland or that has recurred after initial treatments, such as surgery or radiation. Patients with this more advanced prostate cancer receive a therapy called androgen ablation, which inhibits production of testosterone – the culprit that allows a tumor to keep growing.

Though the model's outcomes remain theoretical at this point, the researchers have developed enough of a system to show that their incorporation of some personalized data – details about a patient's tumor cell characteristics in particular – would give doctors more than they currently have to work with in making decisions about this stage of treatment.

"The model in its current form is proof of the concept that we can capture all of these different outcomes that are observed clinically. But we still need to refine the model with as much individual data as we can obtain," said Harsh Jain, a postdoctoral fellow in Ohio State University's Mathematical Biosciences Institute and lead author of the study.

"We envision that this model would be useful for clinicians who could

keep feeding the equations with data about how a patient is responding to therapy, which would offer clues about how his cancer cells are mutating. Once you have an idea about that for the short or medium term, the model could predict the optimal therapy for that patient," Jain said.

The model is described this week in the online early edition of the *Proceedings of the National Academy of Sciences.* Jain conducted the work with co-authors Steven Clinton, professor, and Arvinder Bhinder, assistant professor-clinical, in Ohio State's division of medical oncology, and Avner Friedman, a Distinguished University Professor at Ohio State.

Prostate cancer is diagnosed in about 240,000 American men and leads to about 34,000 deaths each year, according to the National Cancer Institute.

The treatment of this cancer in its more advanced stages brings about chemical castration by targeting one of several mechanisms involved in the production of testosterone. In most patients, cancer cells develop castration resistance over time – on average, between 1½ and two years after the start of treatment. However, the overall range of resistance development spans from a few months to more than 10 years.

Jain said that some scientists have proposed that this treatment leads directly to castrate-resistant disease because once testosterone is removed from the body, mutant cancer cells that can survive in a no- or low-testosterone environment are able to take over the tumor.

Currently, continuous treatment to eliminate testosterone is the standard of care. But because clinicians know castration resistance is inevitable, a new approach is under study. A national clinical trial is assessing the benefits and risks of intermittent androgen ablation – keeping patients on the drugs until symptoms improve, and then giving men time off from

the medication until the disease begins to progress again.

The math model developed by Ohio State scientists suggests that based on average clinical data currently available, such intermittent therapy could actually accelerate the development of castration resistance.

"In the same way that intermittent use of antibiotics gives a chance for bacteria that are resistant to the drug to take over, you might actually end up with intermittent anti-androgen therapy even more positively selecting for mutating cancer cells," Jain said.

However, the averages don't always apply, which is why the scientists are pursuing a system of differential equations to account for individual differences. For example, the "normal" levels of prostate-specific antigen, or PSA, in men's blood cover a fairly broad range, Jain noted. Yet the PSA test remains the most common screening method for prostate cancer, and is used to gauge the effectiveness of treatments in advanced stages, as well.

"The PSA ranges are massive. It's a very heterogeneous thing," Jain said. "When we are talking about cancer, our point is that those variables should be personalized. Everyone's cancer grows differently.

"There are a lot of questions. If you take an intermittent therapy route, how do you decide the scheduling of treatment? Is it based solely on PSA levels? Shouldn't there be some incorporation of personal patient characteristics into these treatment decisions? Can you identify a subgroup of patients who are predicted to respond well to this, or are there conditions when one treatment vs. another could actually make things worse?"

Math offers some answers. The model's foundation is based on existing animal and human data on prostate cancer characteristics. Beyond that,

the researchers have selected parameters to plug into the equations that more specifically detail what could be going on in an individual tumor: cancer cell growth rates, cancer cell death rates, the level of activation of PSA in tumor cells, and how quickly one person's PSA can travel from the prostate to the bloodstream.

The scientists even took into account the competitive power of individual types of cancer cells – for example, some mutated cancer cells aren't as strong as their normal cancer cell counterparts. In those cases, the math model predicts, the best treatment option would be intermittent therapy because the stronger normal cancer cells would keep mutant cells in check during time off from the medication. With the cancer consistently dominated by cells that rely on the presence of testosterone, the treatment would continue to target those stronger cells that respond to androgen ablation therapy, Jain explained.

"That's an important question with any therapy – is it making things better or worse in terms of allowing mutated cells to take over?" he said.

Jain and colleagues are now working to boost the model's power by adding parameters that account for the blood vessel architecture in prostate tumors, a major indicator of how persistent the cancer will be. They also plan to add hundreds of individual patients' case study data to make its predictions even more authentic.

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