Stephen Pennington likes to work backwards. He and his colleagues at the Conway Institute in Dublin have been investigating a number of diseases, most notably prostate cancer.

“The key for us has been to start at the end of the process and identify what type of tests clinicians would most like to have,” Pennington says.

To that end, they mapped the decisions a urologist or molecular oncologist might need to make when treating an individual with prostate cancer—and noted where, at the moment, they find it difficult to make those decisions because they lack vital information.

“Tests that could provide the missing information would be appropriate tests for clinical use,” Pennington says, “and an appropriate goal for our research.”

What the team learned in regard to prostate cancer is that there are two key clinical questions:

“One was establishing whether the disease was significant—that is, would the individual who has it be likely to die from the disease?” Pennington says. “Many men who have prostate cancer don’t die from the disease. They die with it but from something else.”

If the disease is significant in that sense, then the second question is how far has it progressed?

“You would want to know whether the disease has spread beyond the prostate,” Pennington says. “If it has, there’s relatively little curative value in removing the prostate. But if it remains confined to the prostate, then removing it is a sensible strategy.”

In short, establishing whether the disease is confined to the prostate, or not, would be an extremely valuable piece of information to have.

Talks with doctors also revealed how the information should NOT be obtained.

“It was very clear, very quickly, that a tissue-based biopsy test would not be appropriate,” Pennington says.
Prostate cancer is very heterogeneous within the tissue, and doing a biopsy of the prostate really doesn’t sample that heterogeneity, he explains. Around 25 to 30 percent of the time, surgery reveals that the results of a biopsy were inaccurate.

“We quickly realized that doing experiments on prostate tissue wouldn’t allow us to identify markers that would be clinically useful, because any kind of tissue-based test was going to be prone to those same issues,” Pennington says.

Besides, biopsies are unpleasant, to put it mildly, and there’s always the risk of infection or bleeding.

“Our approach to marker research has allowed us to devise a strategy to develop an alternative test—and that is to have the test be blood-based, because ideally it should be noninvasive,” he says. “The test should also be easily repeatable, as a blood test would be.”

“The key challenge in developing a blood-based test is accessing the broad dynamic range of the proteins that are present in serum and of having assays that can cope with that kind of dynamic range. A key step for us has been establishing the Agilent partner lab in which we’ve been able to get really robust, reproducible data,” Pennington explains.

“We identified a panel of proteins and developed MRM [multiple reaction monitoring] assays. We then evaluated—validated would too strong a word for it—the panel’s potential for distinguishing organ-confined from non-organ-confined disease. We did that using two separate cohorts of patients in a randomized and blinded manner.”

In his typically understated way, Pennington says the panel has shown some potential. (Translation: It could well be the basis for the desired blood test.)

Pennington and his team are now working to secure funding to validate the panel using a cohort of about 900 patient samples.

“If all goes well,” he says, “clinicians and patients will have access to an important piece of additional information.”