

Dr. Jason Bielas develops technique to detect rare gene mutations for earlier cancer detection.

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By Fred Hutch staff

One in a million: Dr. Jason Bielas' new technique to detect rare mutations holds great promise for understanding and detecting cancer

CypherSeq, a new method developed by Fred Hutch's [Dr. Jason Bielas](#) to accurately detect unique mutations in specific areas of the genome, is 100 to 1000 times more sensitive than other approaches. In a [study](#) published online in *Nucleic Acids Research*, Bielas and his team demonstrated that they could accurately detect a single gene, which carried a hallmark cancer mutation, among millions of unmutated versions of the same gene.

"CypherSeq has very broad applicability," said Bielas, a researcher in Fred Hutch's Public Health Sciences and Human Biology divisions who studies the implications of nuclear and mitochondrial mutations in cancer development. Bielas plans to apply the technique to problems as wide-ranging as cancer-risk stratification and early detection. He also aims to use it to better understand how exposure to certain mutagens — like cigarette smoke — leads to cancer.

Bielas and Drs. Jessica Bertout and Mark Gregory, postdocs in his lab, put CypherSeq through its paces by employing it to detect rare mutations in a gene called p53, which is mutated early in ovarian cancer. They were also able to paint a picture of the spectrum of mutations that arise in yeast cells, either spontaneously or after exposure to a mutagenic chemical.



Dr. Jason Bielas
Fred Hutch file

Bielas and his team are working to apply CypherSeq to detect ovarian cancer in its earliest stages based on cells from a Pap smear. One [study](#) using a less-sensitive method could detect mutated ovarian cancer cells in Pap smears from about 40 percent of women with advanced disease. Bielas thinks CypherSeq has the potential to raise the detection rate to 100 percent — and to detect ovarian cancer at its earliest stages. "We are hopeful that our enhanced method could be used to detect previously undetectable ovarian cancer, earlier, and at a stage when surgical intervention is curative," he said.

Bielas hypothesized that with the ability to catch incredibly rare mutated cells, CypherSeq could also be applied so that oncologists could use hallmark mutations to identify cancer cells shed from a broad range of tumors in blood samples. It might then be possible to detect many tumors in the earliest stages or detect a recurrence long before worrisome symptoms appear and when treatment options have the most potential to increase survival.

Methods to detect very rare mutations — like those that occur in the rare cancer cell shed from a tumor into the blood, or the random mutation that each cell will pick up as part of normal DNA replication — were previously impossible to track with next-generation DNA sequencing, as the methods themselves are error-prone. Previously, researchers found ways to overcome this error rate to a degree — allowing them to pick out the mutated cell from about 5,000 other cells, for example. But most unique mutations, whether or not they are a hallmark of a tumor cell, will be much rarer. But now, these mutations are detectable by CypherSeq.

"[With CypherSeq] we have the ability to sequence with essentially zero errors, and we can enrich 'target sites' within the genome," Bielas said. This ensures that, when hunting for mutations arising from cancer cells, "we only measure those that originate from the tumor," he said.