“In the last 18 months,” said Richard P. Lifton, MD, PhD, Sterling Professor of Genetics and Professor of Medicine (Nephrology), “science related to cancer has changed drastically.” The reason is a revolutionary breakthrough pioneered at Yale by Dr. Lifton: the ability to rapidly, inexpensively, and accurately identify mutations in tumor tissue using whole-exome sequencing.

It’s well known that most cancers are driven by so-called somatic mutations—alterations in DNA that occur after conception. But until now, science has only been able to guess which mutations contribute to cancer. Dr. Lifton’s recent research ends the guessing. “We can sequence all the genes in the tumor and see what the actual mutations are,” he explained. “And we can identify which ones are the drivers that cause cancer by finding that the same gene is mutated in different tumors more frequently than would be expected by chance.”

Dr. Lifton demonstrated the power of this new technology during the past year by using it on adrenal tumors associated with hypertension. Using gene sequencing, he discovered that either of two mutations in a single gene account for half of these tumors. A diagnostic blood test to detect these mutations in DNA would identify patients with an adrenal tumor, and they could then be prioritized for surgery and cured.

“This is an illustrative example of how this sequencing technology can take a heretofore very mysterious tumor, about which almost nothing was known about its causation,” said Dr. Lifton, “and identify mutations that explain the tumor’s biology lock, stock, and barrel.”

The same technology and approach is being applied to cancers. “In the next several years,” said Dr. Lifton, “thousands of patients will have their tumors sequenced, and this will define the genetic landscape of every cancer in the human body.”

He is particularly interested in exploring why some primary tumors turn metastatic while others do not. That information would make an immense difference in treatment regimens. If a doctor knows that a patient’s tumor is unlikely to metastasize, surgery might be enough, with no need for chemotherapy and other painful, expensive treatments. On the other hand, if the tumor has a high likelihood of metastasizing, aggressive treatment could begin right away. “These are specific questions that we can tackle just by sequencing patients who did or did not have metastatic disease,” said Dr. Lifton.

His team is also looking for “the fundamental genetic architecture that underlies these cancers.” He expects to learn if systemic changes in the primary tumor initiate metastasis, and if the mutations that drive tumors to metastasize to the lung, the brain, or the brain differ from one another or are shared among all metastatic tumors. Once the genes are identified, a patient’s treatment can be tailored to the underlying mutation.

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“A Revolution in Cancer Science

Cancer Genetics and Genomics RESEARCH PROGRAM

Richard P. Lifton, MD, PhD