



Memorial Sloan-Kettering Cancer Center

Michael Berger, PhD (left), Agnès Viale, PhD, and David Solit, MD, will lead Memorial Sloan-Kettering's Center for Molecular Oncology.

and many others where it is not currently part of routine care," he says.

The center plans to genetically profile the tumors from every patient with metastatic disease at MSKCC, totaling more than 10,000 patients each year. Solit says the long-term goal is to also analyze the tumors of patients with earlier-stage disease.

Hundreds of tumors have already been analyzed using a test that can screen for mutations in 341 cancer-associated genes. Even in cancers for which genetic profiling is now standard, only a handful of genes are typically sequenced, Solit says.

Some patients are then matched with approved cancer drugs that target the mutations fueling their tumors. Others are enrolled in clinical trials called basket studies that use agents targeted to a specific mutation, regardless of cancer type. Basket studies allow patients with a driver mutation that has not yet been studied in their tumor type to receive a targeted agent.

The center has several basket studies currently under way, Solit notes. One is testing neratinib (PB272; Puma Biotechnology) in patients with a *HER2* or *HER3* mutation, while another is using vemurafenib (Zelboraf; Genentech) in patients with a *BRAF* mutation. "We have already observed some dramatic responses on these basket studies," he says.

Another CMO initiative uses MSKCC's extensive collection of tumor samples to discover new mutations and drug targets. Researchers are, for example, retrospectively analyzing tumors of exceptional responders, patients who had a sustained response to a treatment in a clinical trial in which nearly all other participants did not.

Solit recently discovered that a mutation in *TSC1* was responsible for

an advanced bladder cancer patient's remarkable response to everolimus (Afinitor; Novartis), a targeted drug approved for kidney cancer. Solit is now finalizing plans for a basket study to test everolimus in patients whose tumors test positive for a *TSC1* mutation.

MSKCC is not alone in its quest to bring the genomic revolution into patient care. Earlier this year, San Diego, CA-based Human Longevity Inc. launched a similar effort to understand the molecular underpinnings of cancer and other diseases, as did the Broad Institute of MIT and Harvard in 2004.

What sets the CMO apart is its ability to apply molecular insights in real time to guide clinical practice. "Most of the sequencing that's been reported to date has been performed as part of retrospective studies," Solit says. "The CMO will use next-generation methods to prospectively profile patients who are actively receiving treatment in the clinic now." ■

Glioma a Downside of Long Telomeres

Long telomeres may protect against cardiovascular disease and promote longevity. They may also raise the risk of glioma, a new study in *Nature Genetics* reveals (Nat Genet 2014 June 8 [Epub ahead of print]).

In the popular view of telomeres, longer is better. Indeed, studies have linked truncated telomeres to reduced life span and increased vulnerability to heart disease and stroke. Research on the relationship between telomere length and cancer risk, however, has provided mixed results. For some cancers, including pancreatic and lung cancers, short telomeres correlate with greater susceptibility. For other cancer types, such as colon and breast, the opposite holds true.

Lead author Kyle Walsh, PhD, a genetic epidemiologist at the University of California, San Francisco, and colleagues weren't looking for a telomere connection when they began searching for new single-nucleotide polymorphisms (SNP) associated with glioma. The researchers first searched out SNPs in genotype data from 1,013 glioma patients and 6,595 healthy individuals. They then verified their

findings by analyzing an additional 631 patients and 1,141 controls from independent sources. Most of the patients in both groups suffered from glioblastoma, the most common and most aggressive form of glioma.

The team found that a SNP with a large effect on glioma risk lies near the gene *TERC*, which encodes the RNA component of telomerase, the enzyme that lengthens telomeres. They also analyzed two previously identified SNPs that are located in the genes *TERT* and *RTEL1*, which encode proteins that spur telomere extension. Both SNPs showed a robust association with glioma risk.

To determine the relationship between these SNPs and telomere dimensions, the scientists turned to a 2013 genome-wide association study on leukocyte telomere length in more than 37,000 people of European ancestry. The SNP residing near *TERC* and the SNP in *TERT* showed a strong correlation with longer telomeres. In contrast, the SNP in *RTEL1* was moderately associated with shorter telomeres.

The team also found that other glioma-linked genes, such as *EGFR*, didn't correlate with telomere length. That finding suggests there are multiple mechanisms for glioma development, not all of which involve telomeres.

"We have evidence that for glioma, longer telomeres are a risk factor or are a biomarker for risk," says Walsh. However, researchers did not measure telomere length in glioma patients. If long telomeres do promote the development of glioma, how they accomplish it is unclear.

Walsh notes that *TERT* variants turn up in many kinds of cancer. However, researchers have uncovered cancer-associated variants of *TERC* only in colon cancer, multiple myeloma, and glioma. This similarity between disparate cancers suggests they have a common mechanism that might depend on telomere length, he says. ■

Choosing Biomarkers Wisely

The explosion of genomic data means that scientists who are planning clinical trials can consider more molecular information than ever before. An international team of experts has