

medium and an artistic mode that resonates, Lyons said.

For Green, emphasizing this medium over other narrative forms arose from a combined interest in bioethics, medicine, and the visual arts. The potential of visual storytelling first struck him, he said, after reading *Maus* by Art Spiegelman, which came out in 1986.

“I thought, if you can do a comic about something as extraordinary as the Holocaust, why not medical issues?” Green said.

He now has 5 years of data evaluating students’ attitudes toward reading and creating their own comics, awaiting publication.

“There’s not a whole lot of research out there,” he conceded, but interest is growing.

In June, for the fifth year in a row, an international conference on comics and medicine will take place, this one hosted by Johns Hopkins University Medical School in Baltimore. As an educational tool, graphic novels hold real appeal, Green said.

“So much about being an effective doctor is being an effective communicator,” he added.

So far, graphic novels disproportionately deal with cancer and structural issues, such as access to care or insurance concerns,

that patients face. What’s most remarkable about these stories, he said, other than transcending language barriers and the so-called digital divide, is that they offer a perspective people cannot get in any other way. For example, Marisa Acocella Marchetto’s *Cancer Vixen*, if told by a doctor, would focus on the disease itself, he suggested.

“And yet, what she’s most scared about is not her upcoming treatments but how to pay for them,” he said. “She keeps asking whether the hospital will accept her American Express card.”

Patient Videos

Gregory Makoul, Ph.D., senior vice president and chief innovation officer at Saint Francis Hospital and Medicine Center in Hartford, Conn., said he still favors unscripted patient videos as his primary narrative approach.

“It’s an incredibly powerful tool, allowing patients to film their own stories” in the privacy of their homes, he said. Everyone remembers one clip, which he often shows during speaking engagements, Makoul said. In it, a young woman furiously chops onions in her kitchen as she talks about her doctor’s dismissal of her questions as stupid.

To gauge doctors’ communication skills (or lack thereof), Makoul said, he helped develop and holds the copyright to the Communications Assessment Tool (CAT). Funded by the American Board of Medical Specialties, CAT is now in 20 countries besides the United States and is available free to any health care provider for noncommercial use by contacting him at gmakoul@stfranciscare.org. Originally designed to elicit patient preferences, CAT has evolved to include different measures of how well patients understand what their doctors are telling them and actionable feedback for physicians, according to Makoul.

“The videos reinforce CAT because both are focused on patients’ point of view,” he said, “but CAT doesn’t measure the impact of patients’ narratives.” However, he added, “I do think it’s tremendously therapeutic for patients to tell their stories.”

Fies would agree. Though some criticized him for making fun of his mother’s illness by using a comic format, he said, neither he nor his mother saw it that way.

“I think she saw the comic as her legacy as much as mine,” Fies said. “She got a lot of satisfaction from it.”

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TERT Promoter Eyed With Suspicion and Hope

By Cathryn Delude

Cancer researchers yearning for a robust universal biomarker of malignancy and tumor grade have long found telomerase a tempting candidate. This enzyme maintains the telomeres at the tips of chromosomes in early development and stem cells but is then usually inactivated, allowing telomeres to erode and limiting cell division. Most cancer cells, however, reactivate telomerase in their quest to become immortal.

Current methods to measure telomerase levels for clinical diagnosis and prognosis through DNA, RNA, or protein analysis have technical difficulties, including lack

of reliable antibodies and inability to use in paraffin-embedded tissues, said Uri Tabori, M.D., from the Hospital for Sick Children in Toronto, Canada. In the past year, he and others took a different approach, looking at the promoter for the catalytic subunit of telomerase, telomerase reverse transcriptase (TERT) instead of directly at the gene.

TERT Promoter Methylation

Status in Pediatric Brain Tumors

In that study (*Lancet Oncol.* 2013;14:534–42), Tabori focused on methylation. Although methylation typically silences genes, it

can promote cancer, possibly by silencing tumor-suppressor genes. Also, methylation status can be quickly, easily, and accurately tested in clinical samples. In an initial sample of 280 malignant and healthy pediatric brain samples, TERT promoter hypermethylation characterized 72% of the malignant samples but only one healthy sample. In further analyses of different pediatric brain tumors, methylation predicted survival and progression-free survival, increased in tandem with telomerase expression, and distinguished low-grade from high-grade tumors, as well as which low-grade tumors progressed to high-grade lesions.

That finding was exciting because pediatric brain tumors can be difficult to grade, but the distinction has prognostic and therapeutic relevance, explained pediatric oncologist Scott Diede, M.D., Ph.D., of the Fred Hutchinson Cancer Research Center in Seattle, who wrote a commentary on the study (*Lancet Oncol.* 2013;14:447–8).

“Most low-grade tumors don’t progress, so we wish we could figure out up front which rare tumor we need to treat aggressively instead of waiting until they’ve become more malignant,” he said.

Astoundingly Recurrent TERT Promoter Mutations

Tabori’s methylation paper was already accepted when two studies of melanoma independently finding highly recurrent DNA mutation in the TERT promoter appeared (*Science* 2013;339:957–9 and [in same issue] 959–61). About half of melanomas have driving mutations in an oncogene called BRAF, which the inhibitor vemurafenib now targets.

“We wondered if mutations in non-coding regions might explain some additional portion of melanomas,” said Levi Garraway, M.D., Ph.D., a cancer geneticist at the Broad Institute of Harvard and MIT. An initial quick sweep of 19 whole-genome sequences of melanoma identified two nearby single-base-pair mutations in 83% of tumors of the TERT promoter. In a larger sample, 50 (71%) of 70 melanoma tumors harbored one or the other mutation.

“We were quite skeptical of this prevalence at first because they could be just an artifact of sequencing,” recalled Franklin Huang, M.D., Ph.D., first author of the paper.

But meticulous follow-up studies confirmed the finding in not only melanoma but also liver and bladder cancers. Moreover, the concurrent *Science* paper found a similarly high prevalence of the same two mutually exclusive TERT promoter mutations in melanoma.

“We all expected that sooner or later we would find regulatory mutations that were as important as protein-coding mutations,” reflected Garraway, “but we never imagined

they would be more prevalent than gene mutations.”

A Theme Emerges: Specificity and Age

“That was a monumental discovery,” said Patrick Killela, a Ph.D. candidate in the lab of Hai Yan, M.D., Ph.D., at Duke University Medical Center and first author of another article on TERT promoter mutations (*Proc. Natl. Acad. Sci. USA* 2013;110:6021–6). In this study, Duke researchers and their collaborators investigated the TERT promoter mutations in more than 1,200 tumors of 60 types of cancer. Conducting such a large study quickly was possible because the two “hotspot” point mutations are just 22 base pairs apart, so they could be tested by using PCR on one fragment.

“The numbers just jumped off the page,” Killela said.

“Most low-grade tumors don’t progress, so we wish we could figure out up front which rare tumor we need to treat aggressively instead of waiting until they’ve become more malignant.”

One or the other TERT promoter mutation occurred in 44% of hepatocellular carcinomas, 66% of bladder cancers, 83% of glioblastomas, and 20% of medulloblastomas—always the most prevalent mutation identified to date. The mutations mostly characterized cancers arising from tissues that self-renew slowly. Previously, researchers had identified several mechanisms such cells use to revert to a more stemlike, proliferative state. Now, TERT promoter aberrations were joining that collection.

Mutation specificity in tumor subtypes also was readily apparent. In gliomas, testing for TERT promoter mutations along with another hotspot mutation, IDH1 or IDH2, could distinguish the most common

types of brain tumors: Primary glioblastomas had mutations in TERT only (83%); astrocytomas in IDH only (75%), and 78% of oligodendrogliomas had mutations in both TERT and IDH.

Age of diagnosis also mattered. Whereas 83% of 78 adult primary glioblastoma tumors harbored TERT mutations, only 11% of 19 pediatric glioblastomas did. Likewise in medulloblastoma, typically a pediatric cancer, two of the four subtypes (WNT and SHH) had recurrent mutations, but they were concentrated largely in older patients.

“We were intrigued by their medulloblastoma results,” said pediatric oncologist



Scott Diede, M.D., Ph.D.

Marc Remke, M.D., at the Hospital for Sick Children.

In a later analysis of 446 medulloblastoma tumors (*Acta Neuropathol.* 2013;126:917–29),

this group also found the mutations concentrated in the WNT (11%) and SHH (38%) subgroups, with a striking age-specific pattern particularly in SHH: Less than 9% of infant, 22% of childhood, and 83% of adult SHH harbored mutations.

“Having a new way to further subdivide the SHH group by TERT promoter mutation opens up a new avenue of biology to explore,” said coauthor Vijay Ramaswami, M.D., “and an opportunity for preclinical modeling and targeted therapy.”

Mutations Versus Methylation

What, then, is the relationship between the TERT promoter mutations and the hypermethylation Tabori reported? Are they redundant or alternatives?

“Without knowing about the sequence in the hypermethylation study, we could imagine that DNA methylation was a surrogate for a promoter mutation that they just didn’t know about,” Diede said.

Two studies have now looked at this relationship. The first, led by Koichi Ichimura, M.D., Ph.D., at the National Cancer Center Research Institute in

Tokyo, Japan, found that methylation and mutations independently occur in adult gliomas (some tumors have both methylation and mutation) but that only mutations increased TERT expression (*Acta Neuropathol.* 2013;126:939–41). The second, from Newcastle University in Newcastle-upon-Tyne, UK, analyzed medulloblastoma and observed that mutations and hypermethylation were mutually exclusive and that both increased TERT expression (*Acta Neuropathol.* 2014;127:307–9). Hypermethylation occurred in various degrees in all subgroups, whereas only noninfant SHH featured mutations.

“I’m not surprised by these discrepancies,” Diede said, “because adult glioma is a totally different brain tumor from

medulloblastoma and the pediatric cancers that Tabori’s group had studied.”

Agreeing in an e-mail, Ichimura added, “These studies collectively consolidate the significance of TERT alterations in diverse types of brain tumors, and I expect to see something similar in other types of human cancers too. Our task now is to translate these findings in the clinic to find a way to utilize TERT alterations as a biomarker or therapeutic target.”

But what about that infant SHH, with neither TERT promoter mutation nor methylation, as well as the scarcity of promoter mutations in pediatric gliomas? Perhaps, several researchers speculated, young brain cells already still have active telomerase and do not need any of the aberrations apparently so common among many other brain tumors.

What Else Is Out There?

Just the past year’s cascade of studies, one reacting to another, found an unexpected prevalence of two possibly mutually exclusive TERT promoter aberrations—hypermethylation and point mutations—in multiple cancers. Collectively, these studies validate efforts to move beyond the gene-centric approach to disease research that focuses on protein-coding genes and to embrace noncoding regulatory elements that can initiate and promote cancer.

“We completely missed the TERT promoter in all these years of whole-exome sequencing,” Killela said. “It’s the first promoter we identified, yet it has such significance. How many others are out there?”

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Why Is Breast Cancer Chemoprevention Such a Hard Sell?

By Judy Peres

Antiestrogen agents can dramatically reduce breast cancer incidence. The U.S. Food and Drug Administration has already approved two such drugs, tamoxifen and raloxifene, for primary prevention in high-risk women. Two others, exemestane and anastrozole, appear even more effective at risk reduction.

But despite the recommendation of medical authorities, including the U.S. Preventive Services Task Force, the American Society of Clinical Oncology, and the National Institute for Health and Care Excellence in the UK, only about 1% of eligible women take a chemopreventive agent, according to Jack Cusick, Ph.D., head of the Centre for Cancer Prevention at Cancer Research UK.

Breast cancer chemoprevention remains “an enormously underutilized tool,” said Paul Goss, M.D., Ph.D., director of the Dana–Farber/Harvard breast cancer program. “Compared with statins or

antihypertensive agents, the use of breast cancer chemopreventive drugs is very low, and yet the safety is as good if not better.”

According to breast experts, chemoprevention is a hard sell for several reasons:

- Primary-care providers are not trained in breast cancer prevention.
- Even if general practitioners are knowledgeable, they don’t have time in a 6-minute office visit to ascertain a patient’s preferences, assess her risk, and discuss costs and benefits of reducing that risk.
- Medical oncologists, who are best placed to have those discussions, often don’t think in terms of prevention and don’t see most at-risk women.
- Women fear side effects, and some doctors hesitate to prescribe potentially toxic drugs to healthy people.
- Manufacturers don’t promote the drugs for primary prevention, especially if the drugs are off-patent.

- No simple but accurate way exists to assess breast cancer risk.
- A woman taking a risk-reduction drug has no way to know whether it’s working.

Larry Wickerham, M.D., deputy chair of NRG Oncology (formerly NSABP, the National Surgical Adjuvant Breast and Bowel Project), said he believes that the National Cancer Institute could do more to educate the public about breast cancer chemoprevention.

Promoting Prevention

“Preventive cardiology didn’t exist 30 years ago,” Wickerham said, “but now every cardiologist treats cholesterol and blood pressure. The National Heart, Lung, and Blood Institute did a good job promoting preventive agents, first to the medical profession and then, in a sustained way, to the general public. Most people now know their levels and know the importance of controlling