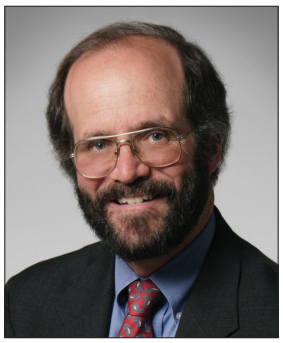
Mark E. Burkard, MD, PhD



Robert N. Golden, MD

Shared Knowledge in Precision Cancer Care

Mark E. Burkard, MD, PhD; Robert N. Golden, MD

John told his oncologist, Dustin Deming, MD, he had no interest in chemotherapy. At age 79, John had survived cancer and chemotherapy a decade earlier, and he now had colon cancer metastatic to the liver. Chemotherapy-related toxicities would have dramatically altered his quality of life, and that just didn't make sense to John. In helping consider alternatives, Dr Deming—the co-leader of the Precision Medicine Molecular Tumor Board (PMMTB) at the University of Wisconsin School of Medicine and Public Health (SMPH)—performed DNA testing of 87 genes from John's tumor biopsy. Surprisingly, his type of colon cancer was driven by a gene called *HER2*—an extracellular receptor that typically drives growth of breast cancer. Dr Deming presented the finding to the PMMTB, which confirmed that this was a good drug target and recommended trastuzumab (Herceptin)—a monoclonal antibody approved for breast cancer that targets and turns off the *HER2* protein. With this information, John decided to undergo the trastuzumab treatment instead of chemotherapy. Over the next 3 months, his tumors shrank dramatically, and he had minimal side effects. His carcinoembryonic antigen (CEA) level plummeted from more than 7,500 ng/ml to 50 ng/ml.

> Advances in technology over the past decade have catalyzed the clinical application of DNA sequencing, allowing it to be routinely and inexpensively performed on hundreds of genes in each patient's cancer. However, using this information can be daunting, given the number of possible genes that may be involved.

Breathtaking progress in cancer therapy provides hope, and it also challenges oncologists to keep abreast of the latest innovations. Today, integrating genomic information into patient care is one preeminent challenge, as it strikes at the very root of traditional cancer classifications. For example, guidelines exist for colon cancer and breast cancer, but not for colon cancer that is genetically similar to breast cancer. To address the challenge and optimize the impact on cancer patients across Wisconsin, the SMPH and the UW Carbone Cancer Center launched the PMMTB as a collaborative endeavor that links oncologists across the state with the diverse expertise of UW-Madison faculty and staff members, at no cost to physicians or patients.

Cancer is a genetic disease in which DNA mutations in specific oncogenes drive the growth and aggressive behavior of tumors. Knowledge of particular mutations can profoundly help some patients, because select drugs can turn off specific oncogenes, leading to tumor regression. Advances in technology over the past decade have catalyzed the clinical application of DNA sequencing,

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allowing it to be routinely and inexpensively performed on hundreds of genes in each patient's cancer. However, using this information can be daunting, given the number of possible genes that may be involved. Even within a given gene, it is possible to have dozens of distinct mutations, only some of which impart functional alterations to the encoded protein. Moreover, the findings of DNA sequencing routinely challenge the very classifications of cancer entrenched through a century of practice and education.

Traditionally, cancers have been classified by their site of origin—breast cancer starts in the breast, and lung cancer starts in the lung. However, DNA sequencing reveals a startling diversity in the genes that drive cancers from a given organ. It also commonly finds unexpected similarities between cancers that originate in different organs. While current cancer treatment guidelines do not encompass recommendations for testing for rare mutations, regulatory bodies—including the US Food and Drug Administration (FDA)—recognize the progress and are in the vanguard of pushing forward clinical applications made possible by this emerging science. In 2017, the FDA, for the first time, approved a drug based on mutations regardless of tumor type. This first-ever *pan-cancer* approval was for the use of pembrolizumab to treat any solid tumor that harbors mutations in genes involved in DNA mismatch repair. A second pan-cancer drug, which targets extremely rare *NTRK* fusions, is being reviewed by the FDA. Others are expected to follow.

Since 2015, the PMMTB has led a bimonthly, web-conferenced statewide tumor board through which physicians can discuss cancer patients, including their tumor DNA testing results. The PMMTB calls upon UW-Madison experts in pathology, genomics, genetic counseling, medical oncology and pharmacy, as well as collaborators, usually medical oncologists, from health systems throughout Wisconsin. The board focuses on helping patients for whom there are no standard treatments known to cure the cancer—typically those whose cancer is metastatic. To date, the PMMTB has reviewed DNA testing and provided specific recommendations for more than 500 patients. Along the way, there have been many unexpected findings. For example, individual breast cancer patients were found to have mutations of *EGFR*, *MET*, *ROS1* and *RET*—mutations found in 10%, 2%, 2% and 1% of non-small-cell lung cancer, but all of which are found mutated in far fewer than 1% of breast cancers. This allowed the respective lung-cancer-targeted drugs to be repurposed for these Wisconsin patients.

There are many opportunities for missteps in selecting treatments. It is important to be aware of clinical trials, basic research and failed drugs related to specific mutations within a gene. Oncologists must recognize that DNA tests can produce false findings. Not all mutations reported in a gene confer functional changes in the resulting protein. Moreover, some mutations can be inherited in families and are not limited to the tumor—a critical consideration that can have profound impacts on the patient's family members.

The implementation of DNA testing in patients also presents practical challenges. For instance, it can be difficult to update standard pathology processes so that advanced DNA testing becomes routine. Payers often do not cover the cost of testing, and some require laborious authorization processes. Current guidelines are silent on when to perform DNA testing in most patients, so physicians often are left to decide with each patient. One common practice is to perform DNA testing only after multiple standard therapies have been exhausted, but this may be too late if the patient becomes too ill to tolerate even targeted therapies. Further, oncologists operating independently might make missteps in selecting drugs, and it may be difficult to share failures or successes with colleagues. Thus, other oncologists may repeat similar, unsuccessful trials due to the missed opportunity to learn from the prior experience of others. By sharing best practices and knowledge, the PMMTB is helping oncologists across Wisconsin avoid such pitfalls, with the goal of making sure patients in the Badger State receive the most advanced and broadest access to precision oncology.

To further these efforts, in 2017 the Wisconsin state government provided support for the PMMTB, which has enhanced its infrastructure. The board now is providing access to more patients, and by creating a database that carefully catalogs outcomes, it is continuously improving the strength of its predictive power.

Not every cancer patient will benefit from precision oncology. Those with potentially curable cancer are best served by stepwise advances in clinical trials or standard treatments. Many patients with incurable cancer have common DNA mutations in genes such as TP53 and KRAS, which are poor drug targets, and mutations in these genes do not help identify the best treatments. However, a significant fraction of those with incurable cancer—people like John—benefit profoundly.

A well-known adage in medicine regarding "hoofbeats" and "horses versus zebras" reminds us that common things are common. However, the experience with the PMMTB's first 500 patients has partially challenged this view. Given the large number of possible genes and mutations involved in cancer, there are thousands of ways that DNA testing can reveal a very uncommon feature of cancer. As shown by the *HER2* in John's colon cancer—and *ROS1*, *RET and MET* in breast cancer—collectively, the uncommon becomes common. Through the PMMTB's ongoing work, every cancer patient in Wisconsin can have access to the most sophisticated, state-of-the-art approach to personalized oncology care.

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