GENOMIC MEDICINE

Breaking the Code

In a recent lecture, Dr. Harold E. Varmus, Nobel laureate, former head of the National Institutes of Health, and president of Memorial Sloan-Kettering Cancer Center, suggested that we should temper our expectations about the near-term prospects for finding "a" cure for cancer. Why would a champion of biomedical and cancer research make such a statement?

BY GREG FEERO, M.D., PH.D.

The comments probably were spurred in part by three recent publications that described the comprehensive genetic analysis of a large set of human pancreatic and glioblastoma multiforme tumor samples. The results, while disheartening from the perspective of front-line clinical providers, affirm that cancer researchers and geneticists won't be out of work anytime soon.

The diversity of genetic alterations in these panels of tumor samples was mind numbing. In the case of pancreatic cancer, the average number of mutations in a given sample was reported to be 63. At the same time, the overlap between mutations in separate samples was minimal—just 24 pancreatic cancers held mutations in more than 1,000 genes. Much the same was found in glioblastoma samples, in which each tumor studied held about 47 mutations on average, but 22 tumors harbored mutations in more than 750 genes.

Several interesting gene associations fell out of the analysis, including confirmation that the gene associated with neurofibromatosis (NF1) is associated with sporadic glioblastoma, and that mutations in the isocitrate dehydrogenase 1 (IDH1) gene are associated with disease in younger patients and in individuals with secondary tumors.

In addition, patients with IDH1 gene mutations had a considerably longer survival (3.8 years vs. 1.1 years) than did those without IDH1 gene mutations. This fact may lead to the ability to provide a clearer prognosis for at least some glioblastoma patients.

One of the brain tumor studies was published as part of the first wave of data from the Cancer Genome Atlas project (cancergenome.nih.gov/about/mission.asp). The pilot phase of this project is examining the genetic alterations that are found in brain, lung, and ovarian cancers. If all goes well, the project will be scaled up to tackle an even larger variety of malignancies.

These studies strongly indicate that working out cures for solid tumors is not going to be as straightforward as targeting the BCR-ABL oncogene in chronic myelogenous leukemia.

Yet despite the daunting complexity of genetic alterations exhibited by the tumors in the three studies, there is hope for developing effective targeted therapies. As it turns out, relatively few pathways are affected by the bewildering array of mutations, and these affected pathways overlap considerably among individual cancers.

This raises the possibility that drugs targeting critical steps in these pathways might have applicability to multiple tumors of any given type and perhaps even multiple types of tumors.

Much more information certainly will come from in-depth genetic analysis of cancer tissue samples, and with the ever-decreasing cost of sequencing technologies, the pace of discovery is poised to become exponential. Network theory is steadily improving our ability to work out complex associations between seemingly unrelated pathways of cellular function. High throughput screening assays for drug discovery are being used more widely to speed drug identification.

Yes, Dr. Varmus is correct to point out that cancer is an extremely complicated constellation of disorders. No, there probably won't be "a" cure for most specific types of cancer, much less all types of cancer. However, we finally have the tools to crack the code, and, more than ever, reason to hope for cures—and perhaps even prevention. ■

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AAFP Eyes Greater Role in Setting CPT Values

BY MARY ELLEN SCHNEIDER
New York Bureau

Over the next year, officials at the American Academy of Family Physicians will weigh the best strategy for getting their voices heard when it comes to setting the values that determine Medicare payments.

Traditionally, organized medicine has come together through a body called the Relative Value Scale Update Committee (RUC) to advise officials at the Centers for Medicare and Medicaid Services on the relative values that should be assigned to CPT codes. But over the past several years, primary care physicians have grown dissatisfied with the process, which has assigned lower values to cognitive services.

Most recently, several state chapters joined to urge that the AAFP either work to gain greater representation on the RUC or leave that body and seek an alternative way to advise the CMS.

That proposal was one of two RUC-related resolutions referred by the academy's Congress of Delegates for study by the board of directors. The board plans to issue a report in 2009.

The RUC is a multispecialty expert panel sponsored by the American Medical Association that advises the CMS on the values that make up Medicare allowable charges. Specifically, the 29-member group makes recommendations on the work- and practice-expense components of the Resource-Based Relative Value Scale (RBRVS) system.

Those recommendations help determine how the multibillion dollar Medicare physician payment budget will be distributed, said Dr. Terry L. Mills Jr., a family physician in Newton, Kan., and the AAFP's advisor to the RUC. The RUC has no formal relationship with the CMS, but CMS officials put a lot of weight on the group's recommendations and have historically accepted their advice more than 90% of the time, he said. "It's the most powerful body in medicine that no one has ever heard of," he stated.

One of the criticisms of the RUC is that it underrepresents primary care physicians. Only 4 of the current 29 RUC members are from traditional primary care specialties. Most of the rest are from specialties dominated by procedural work.

"There's too much self-interest involved" in the RUC process, said Dr. William Gillanders, director of the family medicine residency program at Providence Milwaukie (Ore.) Hospital.

Dr. Gillanders, who is also the treasurer of the Oregon Academy of Family Physicians, said there should be greater representation of primary care physicians in making recommendations on payments issues. However, he said efforts to get the RUC to change its structure voluntarily have failed, so he wants to appeal to the CMS to mandate a change.

He supports a resolution introduced at the Congress of Delegates that would instruct the AAFP leadership to petition the CMS either to develop an independent Relative Value Scale advisory board with membership that is representative of the current physician workforce providing care to Medicare beneficiaries, or to mandate a restructuring of the RUC.

But Dr. Robert Wergin, a family physician in Milford, Neb., who was involved in advocating for changes to the RUC at the recent AAFP Congress of Delegates, favors staying involved in the RUC and trying to work within that process to gain greater representation, and ultimately greater payment, for primary care. If that approach is not viable, then AAFP will need to consider alternatives, he said. By dividing the RUC, primary care physicians would risk having less influence on the payment system, he noted.

There should also be more transparency in the RUC decision-making process, about which little is known, Dr. Wergin said.

However, Dr. Mills argued that it is premature to give up on the RUC, despite the frustration with how cognitive services are valued. "The RUC remains tremendously important," he said.

The greater problem may not be a failing of the RUC, but of the RBRVS system as a whole, Dr. Mills said. That system works well for compensating physicians for procedures, but it fails to account for the complexity of coordinating care for chronically ill patients, he said. It would ameliorate some of the problems if AAFP and others could lobby Congress to change the reimbursement system so that complex management is recognized through a regular chronic care fee, he said.

The AAFP board of directors has already been active in examining the RUC. Earlier this year, the board approved a statement saying that the RUC has "failed" and won't be viable until it is restructured to give primary care proportional representation. AAFP has also pledged to investigate alternatives to the RUC. ■

INDEX OF ADVERTISERS