Genomic Testing: A Struggle for Oncologists

By Karyn Hede

Should doctors present genomics results to patients—and if so, how? Oncologists at Boston’s Dana–Farber Cancer Institute (DFCI) surveyed about their participation in a broad genomic screening program designed to guide treatment expressed divergent views about using the technology.

Many faculty oncologists there felt unqualified to serve as genetic counselors. Further showing the divide, 42% of DFCI providers advocated sharing uncertain genomic test results with patients, even though the research protocol calls for withholding such findings. This variation “nicely mirrors a debate happening nationally and internationally around the return of research results, as well as clinical results,” said Stacy Gray, M.D., a medical oncologist and the study’s lead investigator. “So I was not surprised that we saw such a range of opinions because this is an area where the field is not entirely settled. I think that over time we will probably develop some consensus, but we aren’t there yet.”

The Journal of Clinical Oncology study describing the survey, “Physicians’ Attitudes About Multiplex Tumor Genomic Testing” (doi:10.1200/jco.2013.52.4298), also shows the apprehension of DFCI faculty providers, including medical and radiation oncologists and surgical specialists treating cancer patients, who are uncertain about using genomics. Whereas individual genetic testing identifies single-gene mutations or variants that respond to targeted therapy, such as the BRAF gene in melanoma, multiplex genomic testing can look at multiple variants across hundreds of genes. Of 160 responding physicians, 26% were not at all or not very confident in their ability to base treatment decisions on genomic information, whereas less than 20% were very confident.

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“I struggle with this,” said Roy Herbst, M.D., Ph.D., chief of medical oncology and director of Yale Cancer Center’s Thoracic Oncology Program in New Haven, Conn. Herbst, a pioneer in using genomics in cancer treatment, said that the technology has advanced quickly. Now, researchers not only can look for 10 or 15 genes that have Food and Drug Administration–approved therapies but also can sequence every gene.

“The question is, how much do you do, and what’s important?” Herbst said.

To answer that, Herbst is running the Master Protocol, one of the first clinical trials to codevelop genomic biomarkers and targeted inhibitors. It will use a genomics platform from Foundation Medicine to choose from five drugs to treat squamous-cell lung cancer patients in whom platinum therapy failed. All study patients will be closely matched genomically, and in theory, more likely to respond to the selected therapy, Herbst said. Such trials will become more common if multiplex genomic screening does a better job matching drugs to patient tumors. Ultimately, busy clinicians will need annotated genomic reports to help guide the coming revolution in precision medicine, he said. But it is up to the generation in training now to guide that revolution.

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Gray said her research suggests that clinicians are more likely to look to peers or to published treatment guidelines to help decide the appropriateness of genomic testing. An accessible database summarizing understanding of actionable genomic alterations would be useful, she said.
Toward that end, two institutions have compiled dynamic genomic databases to annotate the evidence supporting use of genomic alterations to guide patients toward appropriate clinical trials. Funda Meric-Bernstam, M.D., a surgical oncologist at the University of Texas M. D. Anderson Cancer Center in Houston, has developed a resource for clinicians. Personalized Cancer Therapy (http://personalizedcancertherapy.org) contains information on alterations of 12 cancer-related genes and their therapeutic implications. She said the research team behind the site expects to add 30 genes this year.

In 2011, Mia Levy, M.D., Ph.D., director of cancer clinical informatics at Vanderbilt–Ingram Cancer Center in Nashville, Tenn., and a team of physicians and bioinformaticians launched My Cancer Genome (www.mycancergenome.org), which describes genomic alterations in 19 cancers and has contributions from 22 institutions. The site includes crucial information on known clinical use of alterations as well as links to the nationwide network of clinical trials testing drugs that target those alterations. But Levy, the site’s principal developer, said that “My Cancer Genome is not trying to be guidelines” and is only a first step toward integrating genomics into the clinic. The next phase of clinical decision support, she said, will involve helping the oncologist do treatment selection among the patient’s other clinical factors, such as medical history, and then incorporating the genomic information. Her group and others, she said, are just starting to explore what that might look like.

But in community-based oncology, in which doctors have access to commercial tests but lack guidelines to drive practice, Gray warns of overusing or misusing genomic tests.

“There probably is a lot more that we could do to help physicians feel comfortable using these new technologies,” Gray said, “but the solution is not abundantly clear.”

© Oxford University Press 2014. DOI:10.1093/jnci/dju172
First published online June 6, 2014

Melanoma Treatment’s Changing Landscape

By Susan Jenks

As treatment options for late-stage melanoma change rapidly, a new strategy that combines two immune-checkpoint inhibitors to render invading cancer cells more vulnerable looks particularly promising.

The combination of ipilimumab and nivolumab holds promise as a treatment advance not only for metastatic melanoma but also for head and neck, renal, and even some small-cell lung cancers, said John Thompson, M.D. Thompson is codirector of the Seattle Cancer Care Alliance and professor of medical oncology at the University of Washington School of Medicine.

“There’s tremendous excitement because of a 50% response rate” in patients with advanced disease—considerably higher than that achieved with any other therapies so far, he said.

Now in phase III clinical trials, the ipilimumab–nivolumab regimen signals a new phase in developing immune-checkpoint antibodies. Such antibodies target proteins in the immune system that are ordinarily involved in restraining or turning off an immune response. According to Thompson, early data on durability of patients’ responses in melanoma could be available by midyear, when the American Society of Clinical Oncology convenes in Chicago, May 30–June 3, for its annual meeting.

Although the drugs target different molecular pathways, he said, the pathways they use to bolster T-cell antitumor activity against these deadly cancers are closely related. Ipilimumab, often referred to simply as “ipi,” blocks the cytotoxic T-lymphocyte antigen 4 (CTLA-4) protein, which slows T-cell activation. Nivolumab interacts directly with cancer cells, blocking the interaction between the programmed death 1 (PD-1) protein on T cells and PD-L1, a ligand that binds to PD-1 and sits on the surface of some cancer cells when they’re under attack.

At the National Comprehensive Cancer Network’s 19th annual conference in Hollywood, Fla., themed “Advancing the Standard of Cancer Care,” Thompson addressed new agents and opportunities for treating melanoma while offering a guideline update (he serves on the organization’s clinical guidelines committee). With the changing landscape for treating these late-stage cancers, he said afterward, revising guidelines can be challenging. But the committee reviews them often, he said, adding new treatment options whenever possible.

One example where reviewers moved quickly to place a new therapy on the “preferred list,” Thompson said, occurred earlier this year. The U.S. Food and Drug Administration granted accelerated approval to the first molecularly targeted combination for inoperable, metastatic melanoma in patients carrying a genetic mutation, known as BRAF. BRAF-mutated melanoma occurs in roughly 38% of patients, Thompson said, although “a large part of the molecular pie is still unknown.”

The combination therapy, targeting both the BRAF mutation and MEK further downstream (N. Engl. J. Med. 2012;367:1694–703), had positive results, Thompson said. Patients had a least 9.5 months of progression-free survival while circumventing the resistance common with a single agent. Moreover, despite common side effects of chills and fever, sometimes requiring patients to stop therapy, he said, far fewer secondary skin