capsule at diagnosis. The results don't surprise Stephen Freedland, M.D., a urological oncologist at Duke University in Durham, N.C. He cites a 1999 study in the *Journal of the American Medical Association* of roughly 300 men with biochemical relapse, which found that the interval between the rise in PSA and clinical metastasis lasted a median of 8 years, with a median of 5 years' additional time remaining until death from metastatic disease.

"The point is that the natural history of recurrent prostate cancer is long and thus there is no need to rush to treat most people," Freedland said.

Nelson concurs and says these data show how clinicians "can exploit the pokey growth rate of most prostate cancers," but he warns that ADT should not be delayed in the minority of men whose PSA levels double faster than every 3 months. Then, he says, metastases can appear within a year and settle in the bones. Once there, they cause excruciating pain and elevate risks for debilitating skeletal problems, such as spinal cord compression. Similarly, experts advise against delaying ADT if relapse occurs within a year after primary treatment, or if patients had been treated initially for high-grade (Gleason score of 8 or more) tumors. Edward Messing, M.D., chair of the Department of Urology at the University of Rochester School of Medicine and Dentistry in Rochester, N.Y., warns that 80% of patients treated with radical prostatectomy for node-positive prostate cancer will experience recurrence. And for these patients, he said, immediate ADT after biochemical relapse is associated with statistically significant improvements in overall survival and lessened pain from metastatic disease. Messing and colleagues published those data in *The Lancet* in 2006.

But Messing emphasizes that just a fraction of the men with biochemical relapse fall into high-risk categories. According to Freedland's research published in the *Journal of the American Medical Association* in 2005, only 6% of men had a PSA doubling time of less than 3 months, for instance. Most of the rest have lower- to moderate-risk profiles, and this is the population for whom the new Harvard study is most relevant.

Managing Anxiety

Joseph Domingo-Domenech, M.D., Ph.D., an assistant professor of pathology at the Mount Sinai School of Medicine in New York, says the findings could be useful for patient discussions about how to respond to biochemical relapse. Rising PSA generates a lot of worry among men who thought they were done with treatment. And according to Domingo-Domenech, many want to begin ADT simply to be proactive.

"When you're in clinical practice, you need to know how to manage anxiety," he said. "With the evidence from this study, we can say, 'This treatment will be more toxic than beneficial to you, and there is no harm in waiting.'"

The challenge is that because ADT reliably lowers PSA levels, "you as the doctor look like a hero if you make them go the other way," Nelson added. That can satisfy patients—and lawyers. But even as ADT drops PSA, it ages patients prematurely and increases odds that they will die from another cause.

"If you're the caregiver, your number-one goal is to make sure that your patients don't die from prostate cancer," Nelson said. "So if they die from something else, you've done your job."

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Identifying Cancer Mutations as Therapeutic Targets

By Anna Azvolinsky

Cancer therapies are increasingly targeting specific molecular pathways and mutations. Molecular testing to identify a mutation expressed in a tumor is becoming common both in clinical research and to gauge whether a patient is eligible for a Food and Drug Administration–approved therapy.

These molecular testing efforts have focused on well-defined pathways that drive tumor growth, such as the phosphatidylinositol 3-kinase (PI3K) and the human epidermal growth factor receptor 2 pathways. And yet researchers are just beginning to understand the genes and pathways important for progression of various tumor types.

Although a diagnostic screening test for a single molecular alteration is increasingly becoming common clinical practice, cancer researchers strive to go beyond this method to provide a wider picture of a tumor's molecular landscape.

Importance of Single-Patient Studies

Although treatment with targeted therapies often works well initially, many patients develop resistance after chronic exposure to an agent that inhibits a cancer pathway.

"It is fairly well established that there are two major resistance mechanisms: acquired and adaptive resistance," said Pau Castel, graduate student in the laboratory of José Baselga, M.D., Ph.D., medical oncologist and physician in chief at the Memorial Sloan–Kettering Cancer Center in New York. "[Patients treated with targeted agents who initially respond] tend to acquire adaptive resistance. Tumors are made up of a spectrum of clones and under targeted therapeutic pressure, one

or several clones are selected that can overcome the drug's inhibition, Castel said.

Baselga's laboratory discovered a common mechanism by which advanced breast tumors with mutations in PIK3CA, the gene that encodes the alpha subunit of PI3K, treated with an inhibitor against PI3Kα, called BYL719, become resistant to the drug. Researchers identified the resistance mutation, loss of function of the tumor suppressor PTEN, by analyzing metastatic tumor samples of a trial patient who had a partial response for 7 months to BYL719 but who eventually died when her disease relapsed.

Castel and colleagues took samples from 16 tumors in the lung, liver, and other metastatic sites. They sequenced the genomes of tumors that had shrunk and the rest that had not responded to the drug and did so for metastatic tumor samples obtained before exposure to BYL719. The loss-of-function PTEN mutation occurred only in samples that had responded to the drug, but not in pretreatment samples from the same metastatic tumor. A similar analysis of nine more patients from the same trial identified the PTEN mutation in two more patients. Researchers presented the data at the 2014 annual American Association for Cancer Research meeting (abstract LB-327: "Loss of PTEN Leads to Clinical Resistance to the PI3Kα Inhibitor BYL719 and Provides Evidence of Convergent Evolution under Selective Therapeutic Pressure").

"For those of us working on new therapy targets, a useful technique is to create a patient-derived xenograft mouse model using tumor samples," said Castel. Researchers then study these models, including those made from lesions that relapsed after therapy, for response to clinically available and experimental therapies in the laboratory to understand which drug or combination treatments could work for patients with that resistance mutation.

"I think this methodology of analyzing a patient's tumors directly to identify important mutations is a powerful tool—it's a relatively fast approach," Castel added.

Through focused efforts such as this, researchers are identifying the same mutations in different tumor types, and clinical trials are switching from tumor type–centric to mutation-centric. At Memorial Sloan–Kettering and other centers, so-called basket studies are being designed to enroll patients with a particular mutation, irrespective of the cancer they harbor, said David Solit, M.D., Memorial Sloan–Kettering medical oncologist and director of the center for molecular oncology.

"I think this methodology of analyzing a patient's tumors directly to identify important mutations is a powerful tool—it's a relatively fast approach."

Data Overload

One goal of precision medicine is comprehensive genetic screening during treatment to identify why a patient stops responding to treatment, allowing for a timely response with a different therapy to reverse resistance and progression. For now, researchers use whole-genome or whole-exome sequencing to look for driver mutations in metastatic tumors, comparing primary with metastatic tumors for mutational changes. But data overload is an issue. Tumors tend to accumulate many additional mutations between early and advanced disease, and knowing which new mutations are clinically important can be complicated and time consuming.

To focus such daunting efforts, researchers are developing tools to home in on the genes most likely to be important in cancer. At Memorial Sloan–Kettering, genomics researcher Michael F. Berger, Ph.D., molecular pathologist Marc Ladanyi, M.D., and colleagues have developed MSK-IMPACT. This genetic test allows researchers to sequence 341 cancer-associated genes. Researchers there have performed the test on more than 1,500 samples from patients to identify both predictive-response genetic biomarkers and mechanisms of resistance.

"We are now using the MSK-IMPACT assay to systematically screen patients for mutations that in clinical or laboratory studies predict response to targeted inhibitors. This will become a part of standard clinical management at our center," Solit said.

Still, such analysis is largely confined to larger academic centers.

"The cost of next-generation sequencing has declined significantly over the past several years, and it is now possible to use these large multigene assays as both clinical and research tools," Solit said.

Pau Castel

However, he continued, few institutions have the resources to perform such tests, partly because insurance companies do not pay for genetic testing for most cancers.

It is early days for broad-access comprehensive sequencing, said Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and professor of pathology at the University of Michigan in Ann Arbor. But he is optimistic that such efforts will become commonplace as costs of sequencing drop and research identifies more clinically important mutations for each tumor type.

"We are moving in this direction with new tools and clinical trials. We need to molecularly monitor patients longitudinally through the course of their disease and as they are exposed to various therapies. Just the primary tumor or archival material is not informative enough," Chinnaiyan said.

Databases To Pool Data

Many efforts are under way to generate cancer genome sequencing and expression data as well as analytical tools to process and compare. The Cancer Genome Atlas, funded through the National Cancer Institute and the National Human Genome Research Institute, sequenced a spectrum of primary tumors and made the data publicly accessible. Since then, several analytical tools that pool data from different sources have emerged, allowing those interested to mine data for comparative analytics. Among the first was Chinnaiyan and colleagues' Oncomine, which began as an academic project and is now licensed to

Life Technologies with free public versions as well as prescriber-only tools.

"The tool allows you to compare your own patient or laboratory data against public-domain data," Chinnaiyan said. "It allows integration and analysis of all types of cancer -omics data, and both the databases and the analytical tools keep evolving."

Similar types of free public tools include the cBioPortal from Memorial Sloan–Kettering and the Cancer Browser from researchers at the University of California, Santa Cruz.

Interinstitutional Collaborations

Employing these types of cancer genomic analytical tools in combination with laboratory experiments, Chinnaiyan, along with Charles L. Sawyers, M.D., of Memorial Sloan–Kettering, is leading a seven-institution effort funded by Stand Up to Cancer to identify the diversity of resistance mutations in patients with metastatic castrate-resistant prostate cancer that are acquired during therapy as well as those mutations that can, a priori, predict resistance to a therapy.

"The project is built around multi-institution data sharing and collaboration," Chinnaiyan said. The goal is to sequence the tumors of 500 metastatic castrate-resistant prostate cancer patients. The team has sequenced 150 tumors so far, according to Chinnaiyan. Although setting up the infrastructure and communication took about 6 months, Chinnaiyan said that the academic institutions have now streamlined the data and analyses.

"This will probably be one of the first multi-institutional clinical sequencing cohorts put together," Chinnaiyan said.

Such efforts are important to prevent overlap of efforts and to allow researchers to learn from each other's studies.

"Our community in general will have to be more open to sharing large data sets as they are generated. There are powers in numbers. The only way to really validate results is to look across other large data sets and similar cohort analyses," Chinnaiyan said.

Although the Cancer Genome Atlas has been instrumental, the data have not been that useful for identifying drug-resistance mechanisms. As clinical sequencing efforts continue, more clinical data are generated. Several organizations, including the American Association for Cancer Research and NCI, are in discussions to create bioinformatics resources, pooling such data, but this has yet to go beyond the discussion stage, according to Chinnaiyan.

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PDQ (Physician Data Query) is the National Cancer Institute's source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:

The PDQ Supportive and Palliative Care Editorial Board published a new summary about the preparation needed by health care providers, patients, and families for the transition to end-of-life care in advanced cancer. A comprehensive review of published literature was performed and the summary was reviewed by external experts in the field before final approval by the Editorial Board. The summary was posted on Cancer.gov on 07/015/2015. To review the summary, please use the following link: http://www.cancer.gov/cancertopics/pdq/supportivecare/transitiontoEOLcare/healthprofessional/page1/AllPages

The **PDQ Genetics of Kidney Cancer (Renal Cell Cancer) summary** was recently updated to include a new section on hereditary leiomyomatosis and renal cell cancer (HLRCC). HLRCC is an inherited syndrome characterized by cutaneous leiomyomata, uterine leiomyomata, and renal cell cancer. This section includes a description of the genetics, molecular biology, clinical manifestations, management, and prognosis of HLRCC. Future directions and therapies under investigation are also addressed.
To review the summary, please use the following link:
http://www.cancer.gov/cancertopics/pdq/genetics/kidney/HealthProfessional/Page2#Section_130

The **PDQ Screening and Prevention Editorial Board** recently completed a major update of the Esophageal Cancer Prevention summary. The Board conducted a review of the published literature and revised the text of the summary and updated the citations. To review the summary, please use the following link:
http://www.cancer.gov/cancertopics/pdq/prevention/esophageal/HealthProfessional/page1/AllPages

The **PDQ Screening and Prevention Editorial Board** recently completed a major update of the Ovarian Cancer Prevention summary. The Board conducted a review of the published literature and revised the text of the summary and updated the citations. To review the summary, please use the following link:
http://www.cancer.gov/cancertopics/pdq/prevention/ovarian/HealthProfessional/page1/AllPages

The **PDQ Colorectal Cancer Screening summary** was recently updated to include a new section on adherence to screening. This section states that there have been problems with screening adherence, especially in low income and uninsured people. There has been concern that some people may adhere less to screening with colonoscopy than with fecal tests. To review the summary, please use the following link:
http://www.cancer.gov/cancertopics/pdq/screening/colorectal/HealthProfessional/page1/AllPages#Section_259

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