Individualized genomic testing allows for tailored cancer treatment, new drug research

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Just like a massive iceberg jutting out of the ocean, many of cancer's genetic underpinnings remain hidden under the surface, impossible to predict or map from above. The foreboding shadows and shapes that appear on CT scans and MRIs – and even in the field that doctors see when they zoom in to look at cancer cells under a high-powered microscope – are just the tip of the iceberg.

Penn Medicine's new Center for Personalized Diagnostics, a joint initiative of the department of Pathology and Laboratory Medicine in the Perelman School of Medicine and the Abramson Cancer Center, is diving deeper into each patient's tumor with next generation DNA sequencing. These specialized tests can refine patient diagnoses with greater precision than standard imaging tests and blood work, all with an aim to broaden treatment options and improve their efficacy.

"We're using the most advanced diagnostic methods to unlock cancer's secrets," says David B. Roth, MD, PhD, chairman of the department of Pathology and Laboratory Medicine. "A tumor's genomic profile is the most critical piece of information for an oncologist to have when they're deciding what therapy to recommend. The results of tests in the Center for Personalized Diagnostics reveal a genetic blueprint of each patient's tumor that is as discrete and singular as a fingerprint."

The Center for Personalized Diagnostics unites top experts in genomic analysis, bioinformatics, and cancer genetics – who use the most sensitive data analysis tools available to identify the rarest of mutations –

with oncologists who treat patients and design clinical trials to test new therapies. Together, their efforts will provide cancer patients with cutting-edge diagnostic and therapeutic options.

The first group of patients who are undergoing testing through the CPD includes those with blood cancers and solid tumors of the brain, melanoma, and lung. Throughout 2013, the tests will be expanded for a wider range of cancer patients. Results are available within two weeks – twice as fast as most commercially available testing panels. All new and relapsed Abramson Cancer Center patients will receive this testing – conducted via simple blood tests and/or biopsy of tumor tissue or bone marrow – as part of their evaluation and diagnostic process. Interpretation of results is communicated one-on-one to patients and their caregivers by physicians and genetic counselors.

In contrast to the CPD's offerings, individual genetic tests – which now proliferate in the marketplace, even for healthy people who may be interested in going on a spelunking expedition through their DNA – are time consuming and expensive to conduct, and they often yield information which is not clinically actionable. When these tests are offered for cancer patients, patients are often left with only a veritable alphabet soup detailing genetic information, with few plans for how to use those findings to conquer their cancer.

Since the CPD began operating in early 2013, however, tests in 80 percent of patients revealed genetic mutations that may be used to alter their treatment course or clarify their prognosis. The results are playing a role in:

- Matching patients with existing therapies designed to target mutations previously associated only with different cancers. For instance, some lung cancer patients exhibit mutations of the

BRAF gene, which is targeted by drug Vemurafenib, initially developed and approved for melanoma. Testing in the Center for Personalized Diagnostics is helping clinicians make new connections that will expand the indications for existing drugs.

- Helping physicians determine which treatments a patient will respond to, or how well they will tolerate a particular treatment. Patients with the blood cancer acute myelogenous leukemia who express a mutation known as DNMT3A, for instance, are known to respond to higher doses of the drug daunorubicin. Learning this type of information prior to beginning treatment can help oncologists select and dose drugs in a way that will reduce side effects and boost patients' quality of life during treatment – and increase their chance of completing their prescribed regimen.
- Identifying patients who are likely to have a poor prognosis if treated with first-line therapies, which allows clinicians to set up a cascade of alternative therapies or, in the case of some blood cancer patients, expedite the search for a matching bone marrow donor.
- Detecting resistance mutations that could slow or halt patients' response to targeted drugs, which allows for custom-designed combination therapies to attack tumors through multiple pathways.

The Center's research agenda operates in parallel with its clinical care mission. Each patient's test results will add to an enormous repository of genomic mutation profiles that, combined with the ability to follow patients over time, will help clinical researchers identify new markers and mutation profiles to better predict the course of an individual patient's treatment response and suggest new targets for therapy. As new mutations are detected and novel treatment options are identified, the gene testing panels will be modified and expanded, creating an evolving, real-time mutation profiling option.

"We see 11,500 newly diagnosed patients each year in the Abramson Cancer, and hundreds of others who seek our help when their cancers have not responded, or have returned, after receiving standard therapies elsewhere," said Chi Van Dang, MD, PhD, director of the Abramson Cancer Center. "A key part of our mission is to provide each of these patients these tests as soon as possible, so that we can quickly tailor a treatment regimen that provides them the greatest chance of a cure."

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