DANA-FARBER/BRIGHAM AND WOMEN'S

CANCER CENTER

Rapid Heme Panel: Faster matching of patients and best treatments for blood cancers

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Introduction

Testing blood cancer specimens for mutations that predict prognosis and response to therapies can be lifesaving. Finding the best treatment plan, without delay, is critical, especially for aggressive forms of leukemia and other hematological cancers. A new test developed at Dana-Farber/Brigham and Women's Cancer Center is enabling physicians to do just that.

Cancer is caused by the cumulative effect of multiple genetic alterations. Even within the same diagnosis, the specific mutation "profile" of a cancer can foretell dramatically different outcomes. Knowing the particular combination of mutations driving a patient's disease can help physicians decide whether to recommend a stem cell transplant, a regimen of certain approved drugs, or enrollment in a clinical trial.

Physician-scientists at Dana-Farber/Brigham and Women's Cancer Center have developed Rapid Heme Panel, a quick-turnaround test that puts this crucial information into physicians' hands faster. Rapid Heme Panel focuses on a group of genes that have been linked to blood cancers. Instead of sending multiple tubes of a blood or bone marrow samples to different laboratories that may take several weeks to produce a result, Rapid Heme Panel is performed in-house on a single blood sample and returns results in five business days or less.

Rapid Heme Panel uses next-generation sequencing to identify single mutations or DNA alterations in 95 genes that are frequently mutated in blood cancers, making it the most comprehensive, swiftest blood cancer mutation test available today. It allows oncologists to:

- Establish and refine diagnoses, including distinguishing between blood cancers and other non-malignant blood disorders;
- Rapidly detect genes with important prognostic implications that are useful in treatment planning, such as deciding between consolidation chemotherapy and stem cell transplantation;
- Identify patients who may be eligible for clinical trials, including early-phase trials of new targeted therapies.

The Rapid Heme Panel test is currently being used for adult patients with leukemia, myelodysplastic syndromes (disorders marked by poorly formed or dysfunctional blood cells) and myeloproliferative neoplasms (disorders usually

characterized by high blood cell counts). The Dana-Farber/Brigham and Women's Cancer Center team is now developing similar tests for use in other blood cancers.

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Background – Blood cancer mutation testing

Over the last few years, understanding of the types of genetic alterations that lead to myeloid and lymphoid malignancies has increased tremendously, as have the number of therapeutic agents designed to target these alterations. Scientists have discovered a growing catalog of genetic abnormalities in these malignancies including mutations, rearrangements of chromosomal segments, variation in the number of copies of a gene, and gains or losses of chromosomes. The repertoire of these changes in an individual's cancer can aid physicians in evaluating the patient's risk.

Increasingly, mutation testing is integrated into the care of patients with blood cancers. Acute myeloid leukemia (AML) – the most common acute leukemia in adults – occurs in different subtypes with wide variations in prognosis and treatment. Patients with certain genetic alterations are likely to respond well to available therapies, while those with different DNA changes are at high risk of chemotherapy resistance, and others have an intermediate prognosis. Patients in specific risk categories may do better with certain drugs or with stem cell transplantation.

To help assign patients to different levels of risk, it has been standard practice to test AML blood samples for mutations in the *CEBPA*, *NPM1*, and *FLT3* genes. Before Rapid Heme Panel, oncologists would collect as many as six vials of a newly diagnosed patient's blood or bone marrow and dispatch them to several outside laboratories for separate testing. As much as two weeks might elapse before all the results came back. To physicians treating very sick patients, the lag time was too long and the process too cumbersome. The need for quicker information was urgent.

Development of Rapid Heme Panel

Hematologists/oncologists at the Dana-Farber/Brigham and Women's Cancer Center and the molecular pathologists/hematopathologists at the Center for Advanced Molecular Diagnostics (CAMD) in the Department of Pathology teamed up to design and implement the Rapid Heme Panel.

It was a challenging task made easier by the existing molecular testing platform developed for Profile, Dana-Farber/Brigham and Women's Cancer Center's genotyping research program that sequences 305 genes implicated in a range of cancer types. CAMD performs tumor genetic profiling on samples from all consenting Dana-Farber/Brigham and Women's Cancer Center patients and stores the results in a research database, while returning clinically relevant mutation findings to patients and their providers.

Profile, however, is not designed for or capable of the short turnaround time necessary for a routine clinical test needed by hematologists-oncologists – and one that would be less costly than the multiple tests used in standard practice.

The expertise of Dana-Farber/Brigham and Women's Cancer Center specialists is crucial to the accurate interpretation of results, as well as explaining to other caregivers what Rapid Heme Panel findings mean for providers and patients.

A patient case study

An 18-year-old male patient was referred to Dana-Farber/Brigham and Women's Cancer Center with relapsed refractory acute lymphoblastic leukemia (ALL) with ambiguous immunophenotype. Results from Rapid Heme Panel testing, which were delivered in three days, demonstrated early T-cell progenitor (ETP) ALL associated with driver mutations in the Notch and JAK/STAT signaling pathways. Salvage therapy with the chemotherapy agent nelarabine was attempted, but the patient's disease had no response. Based on the Rapid Heme Panel results, the patient was then enrolled in a NOTCH inhibitor trial (BMS-906024) to provide tailored therapy for his specific disease.

Summary

Rapid Heme Panel was launched in August 2014 and has been used in the diagnosis, prognosis, and treatment decisions for more than 100 patients in just three months. Using Rapid Heme Panel to detect "actionable" mutations, some patients have been enrolled in clinical trials earlier than ever before, say oncologists.

Testing with Rapid Heme Panel can be carried out multiple times during the course of the disease; physician-scientists plan to use the repeated tests to track the frequency of mutations to determine which ones are present for the duration of the disease, and which may be the cause of disease relapse.

Dana-Farber/Brigham and Women's Cancer Center is a leader in precision medicine research and in bringing these tailored therapies to patient care. Investigators here have a strong record of innovation and expertise in the challenges of creating genomic tests and interpreting the results. Rapid Heme Panel, with its unprecedented scope and turnaround time, reflects these researchers' abilities to apply precision medicine in novel ways.