# Updates of Molecular Testing in T-Cell Malignancies

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**Julie McDowell:**

Evolving molecular technologies and genomic knowledge have significantly changed the diagnosis and management of T-cell malignancies. More and more clinical laboratories have adopted next generation sequencing, or NGS platforms to assess clonality and to identify diagnostic and predictive biomarkers.

However, current standard testing practices to diagnose T-cell lymphomas use clonality assessment by fragment analysis. This approach has low sensitivity and low specificity, among other limitations, explains Dr. Jinjuan Yao, a pathologist at Memorial Sloan Kettering's Cancer Center, and a member of the CAP Personalized Healthcare Committee.

Dr. Yao has written an article about how using NGS techniques allow more accurate initial diagnosis, as well as high sensitivity for detecting minimal residual disease, and therefore improving post-treatment outcomes, as she'll explain in this podcast interview.

Hi Dr. Yao. Let's begin with an explanation about the prevalence of T-cell malignancies, and their potential presentations in patients.

**Dr. Jinjuan Yao:**

Thanks for the question. T-cell malignancies include T-cell leukemia and lymphomas. The estimated prevalence rate is 5.3 per 100,000 persons, and the overall prevalence is well below 200,000 cases. And the T-cell lymphoma makes up less than 15% of non-Hodgkin lymphomas in the United States.

Patients' potential presentations include lymphadenopathy, hepatosplenomegaly, cytopenia, and related symptoms such as recurrent infections, bleeding, and the fatigue. Cutaneous T-cell lymphomas may have patch, plaque, tumors and ulcer formation.

**Julie McDowell:**

Now, what led to your interest in this subject for research?

**Dr. Jinjuan Yao:**

As a molecular pathologist with almost 10 years experience of reviewing and assigning out clonality studies of T-cell malignancies, I noticed that current gold standard biomark tool by fragment analysis is often subjective, and quite difficult to interpret in many cases, based on the criteria used in the ratio of the peak heights between the possible clonal peak, and the third last peak in the polyclonal background.

With the advances of next generation sequencing technologies in molecular diagnosis as you mentioned, our laboratory started to validate the NCS CLONALITY testing a few years ago by identifying specific clonal sequences. NCS offers better sensitivity in the specificity, in comparison to fragment analysis in T-cell receptor clonality assessment.

The unique diagnostic clonal sequence can be checked in post-treatment samples for minimal residual disease assessment, MRD, with the limit of detection as low as 0.001%. Those prior challenging cases can now be diagnosed more definitively by separating the applicants with the same size, but different sequences, and the NGS MRD assay can detect early relapse more sensitively than other techniques. I was very excited about this improvement, and decided to do research in this area.

**Julie McDowell:**

You cited results from a couple studies in your article, but your own unpublished data indicated that stricter criteria would lead to fewer false positives. Why is that?

**Dr. Jinjuan Yao:**

We have been monitoring the performance of NGS assay by side-by-side parallel testing with fragment analysis. And we also combine patients' lab results with clinical presentations and disease process. We realized that using more strict diagnostic criteria is very critical to avoid overcall a dominant sequence as a clonal sequence, so that the clinical team will not treat the patient based on the part result of T-cell clonal rearrangement study alone.

Our criteria were initially established with the validation study of around 150 cases, including both positive and negative cases. Then we keep monitoring the assay while it is in clinical application. We modified the diagnostic criteria to increase the requirement to call a clonal rearrangement, both the percentage of top clone and the ratio between the top clone to the background.

This is very important, because some of the post-treatment monitoring cases will be called as clonal rearrangement with the published criteria. The reason that we can identify this issue is because that we validated T-cell clonality MRD study, and we check both the diagnostic sequence and whether there are new clonal sequence in the MRD samples.

By combining all the laboratory results and the clinical features, we finalize the current rules of clonality testing of T-cell rearrangement by NGS. This way we can avoid to call them clones, or possible clones, based on the published criteria. Those could be false positive.

**Julie McDowell:**

What sort of diagnostic value did the various genetic combinations reveal by testing offer?

**Dr. Jinjuan Yao:**

The diagnosis of T-cell malignancies is challenging not only to oncologists but also pathologists, especially at early stage of the disease. With a combination of both clonality testing and genomic profiling by NGS, we have the ability to look for diagnostic biomarkers in evidence to support the clonal process of the abnormal T-cell population. This information will assist the clinical team in patient management, diagnosis, treatment, and follow-up.

**Julie McDowell:**

Finally, Dr. Yao, what should pathologists expect in upcoming research related to T-cell malignancies?

**Dr. Jinjuan Yao:**

Research related to T-cell malignancies are quickly evolving. However, all the research data has to be proved to be solid and clinically relevant before pathologist, either surgical or molecular pathologist, can adopt the new findings in their daily practice. We can anticipate that more pathopneumonic genomic alterations will be applied in the diagnosis and the classification of T-cell malignancies, similar to what we do to use ALK rearrangement in the diagnosis.

In addition, NGS based clonality testing will be more and more widely used, due to its better sensitivity and its specificity, and unparalleled advantage in MRD detection in T-cell malignancies. Thank you.

**Julie McDowell:**

Thank you, Dr. Yao. Dr. Yao's article is entitled The Updates of Molecular Testing in T-Cell Malignancies, and can be found in the Precision Medicine section of cap.org. To locate the article, please search for precision medicine in the search function on the CAP homepage, or visit the member resources section of the site for a link to the Precision Medicine page.

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