# Cancer Immunotherapy Biomarker Testing - What Pathologists Need to Know

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**Julie McDowell:**

Cancer immunotherapy has revolutionized oncology through dramatically increased survival rates even in late-stage disease. Some biomarkers are already covered in what has become routine testing in many laboratories, affording pathologists and opportunity to play a central role in developing and implementing these biomarkers and ways to improve patient care, explains Dr. Eric Walk, chief medical and scientific officer and senior VP of medical and scientific affairs with Roche Diagnostics in this CAPcast. Dr. Walk recently wrote an article on this topic, which is posted on cap.org, under the Precision Medicine Resource Center. Dr. Walk, in your article you refer to cancer immunotherapy as a revolution in oncology. How is this different from the targeted therapy resolution in the early 2000s, and why should pathologists be excited about it?

**Dr. Eric Walk:**

Thanks, Julie, and thanks very much for having me join this podcast. Really glad to be here. In my opinion, it's completely fair to use words like revolution and transformational when talking about cancer immunotherapy because of the truly unprecedented patient outcomes that we're seeing with this relatively new form of therapy. We have now multiple independent clinical trials, all of which demonstrate that cancer immunotherapy is delivering durable overall survival benefits that we just haven't seen with chemotherapy or targeted therapy in the past. For example, we now have 5 to 10 years of clinical outcome data with some of the early immunotherapies, and it's clear that around 20 to 30% of patients experience long-term survival, with a plateauing of the Kaplan-Meier survival curve, and this may represent incredibly a true cure of their disease, which again, we haven't seen in the past.

When I personally attend cancer conferences, I'm tremendously inspired to hear clinical stories being told at these conferences. For example, Dr. Steven Rosenberg at the NCI provides periodic updates on his effort to treat cancer patients with adoptive T-cell therapy, which is a form of immunotherapy where the patient's own tumor directed lymphocytes are harvested, expanded, and then given back to them. Dr. Rosenberg has over the years documented numerous cases of metastatic cancer patients, for example metastatic melanoma patients, who started with widespread metastatic disease. Many of these patients were in hospice. They received this adoptive T-cell immunotherapy and in some cases just one dose of it, and then 10 years later have no evidence of their disease whatsoever and likely are cured of their disease. So this is incredibly exciting progress for the field of oncology and of course for cancer patients.

But why should pathologists be excited about this? In my opinion they should be tremendously excited because pathologists have an absolutely critical role to play in helping select the right patients for the right cancer immunotherapies. Unfortunately today the vast majority of patients don't respond to cancer immunotherapy, and therefore, at least in the short term, there's an urgent need to develop, validate, and implement cancer immunotherapy biomarkers to aid in the selection of patients who will benefit. So therefore I see pathologists as leading all of these activities and therefore very much at the center of the cancer immunotherapy revolution.

**Julie McDowell:**

Now your article reviews several common cancer immunotherapy biomarkers used as a basis for test selection and pathology. You also state that clear guidelines for cancer immunotherapy testing aren't available. What can the laboratory community do about this right now?

**Dr. Eric Walk:**

Right. So first, in addition to the web article, I do invite the listeners of the podcast to review the full article, which was published in Archives of Pathology and Laboratory Medicine. That article is entitled The Cancer Immunotherapy Biomarker Testing Landscape. And I'd also like to take the opportunity to acknowledge my co-authors, Dr. Yohe, Beckman, Schade, Zutter, Pfeiffer, and Barry on the CAP PhD committee for their terrific work and collaboration on that article. So to answer your question, my advice to the laboratory community is to be aware of the cancer immunotherapy biomarkers designated as routine in that article that I just mentioned, but also to stay current on the developments in this evolving cancer immunotherapy space, because the field is moving incredibly quickly.

New immunotherapies and biomarkers are being approved each year, sometimes each month. For example, since the writing of the print article, TMB, tumor mutational burden was approved as a companion diagnostic in association with immunotherapy. Pembrolizumab for TMB high solid tumors. February 5th, 2021, the FDA approved a new CAR T therapy for relapse refractory large B-cell lymphoma. So my encouragement to pathologists and lab professionals is to follow not only pathology literature and conferences, but also oncology sources of information. For example, there are now several cancer immunotherapy dedicated journals and scientific conferences that represent great ways to stay current on this rapidly expanding field.

**Julie McDowell:**

For PD-L1 you indicated that scoring measure and the positivity threshold can vary by combination of assay therapy and indication. How often do these change?

**Dr. Eric Walk:**

So this is an extremely important point. As I discussed in the article, there are four separate PD-L1 assays that have been approved by the FDA in association with four approved anti PD-1 and PD-L1 therapies, and that's across multiple cancer indications. This then creates multiple distinct therapy indication and test combinations, each of which has been approved based on a registrational clinical trial that clinically validated each treatment scenario. So for those who'd like to see a complete listing of the drug and diagnostic approvals, I direct them to tables one and two of the article on the CAP personalized medicine webpage. It's a helpful resource and a quick reference. And some of these approvals represent accelerated approvals that require follow-up confirmatory clinical data, and in some cases, the FDA has enforced changes to cancer immunotherapy drug and diagnostic labels based on this emerging data.

An example of this is back in June of 2018, the FDA drove changes to the labels of two cancer immunotherapies in a way that made PD-L1 a mandatory companion diagnostic for pembrolizumab and atezolizumab. This was based on new survival data in PD-L1 low patients from two ongoing clinical trials. So to answer the question, even though it's not common, pathologists and lab professionals need to stay current on the latest versions of the approved drug and diagnostic labels because occasionally these do change. For diagnostics I can suggest that people visit the diagnostic package inserts and be familiar with them. Those are readily available online. For the cancer immunotherapies themselves the FDA maintains a good website with the latest drug approvals and labeling changes and safety information, and the title of that webpage is the Hematology Oncology Approvals and Safety Notifications page.

**Julie McDowell:**

Now your article also talked about four common biomarkers. Are there any up and coming biomarkers that our audience should consider in the near future?

**Dr. Eric Walk:**

So just as a recap, in the web article on the precision medicine webpage for CAP, the web article covered PD-L1, MMR, MSI, and PMB. The full archives article that I mentioned previously then expanded the review to include POLE1 and POLD1 mutations, pills or tumor infiltrating lymphocytes and immune phenotyping via multiplexing, transcriptional signatures, resistance biomarkers, and the microbiome. Of these, the one that I'm actually most excited and personally interested in is TIL assessment, or tumor infiltrating lymphocyte assessment via multiplexing. And what's really interesting about the TIL space is that pathologists for decades have recognized that tumor inflammation exists. They've been seeing this inflammation through the microscope on H&E slides. But it's only recently that we've realized that the pattern and character of these tumor immune infiltrates may hold critical information relevant for the treatment of patients with cancer immunotherapy.

A really exciting development in this space is so-called immunophenotyping, where we can go beyond H&E morphology to quantify and characterize the specific types of immune cells that are present or absent from tumors such as cytotoxic T cells, regulatory T cells, M1 and M2 macrophages, dendritic cells, NK cells, et cetera. So in addition, the advances that have been made in multiplexing technology now enable pathologists to simultaneously assess multiple immune cell markers and how they colocalize with cancer immunotherapy response markers like PD-L1 and others, with the hypothesis here being that the right combination of markers will increase our ability to predict patients who respond to cancer immunotherapy. Many of these marker accommodations are being explored as we speak in clinical trials, and it's fair to say that there's a bit of a race at the moment to find this magic combination of biomarkers that correlate best with patient outcomes, and I expect that we'll see some more data emerge in this particular area over the next couple of years.

**Julie McDowell:**

Finally, Dr. Walk, you concluded that pathology could be a center of excellence for immunotherapy biomarkers. Do you have any recommendations for pathologists to go about establishing that reputation?

**Dr. Eric Walk:**

Absolutely. First of all, I believe pathologists are already functioning as the personalized healthcare or precision medicine center of excellence. So it's really a logical extension to have pathologists drive the future of cancer immunotherapy biomarkers. There are many ways for pathologists to contribute to this exciting field, and as I mentioned earlier, it's rapidly evolving as well. And these opportunities include the discovery of new cancer immunotherapy biomarkers in academic research by pathologists, the translation of new cancer immunotherapy biomarkers into robust solutions that can actually be implemented into clinical practice in a routine way, driving the adoption of new technologies and assays into pathology practice day in and day out. The training of pathologists on new cancer immunotherapy assays is also important. And finally, in my opinion, pathologists can be the leaders of technology and healthcare information integration that I personally believe will be critical to take cancer immunotherapy to the next level.

One example here that I can cite is Christian Blank and Ton Schumacher from the Netherlands Cancer Institute published a cancer immunotherapy vision piece, if you will, in Science, and they refer to that as the cancer immunogram. And in that article, they described seven classes of cancer immunotherapy biomarkers that they feel are critical for immune responsiveness. And I think this cancer immunogram model could represent a template for how pathologists report cancer immunotherapy biomarkers in the future, integrating assay technologies and biomarker data into a simple diagram that could exist within the pathology report of the future and could be used directly for the most informed clinical decision for the patient. So in summary, I'm tremendously excited, enthusiastic about the expanding role pathologists will have in this ongoing cancer immunotherapy revolution.

**Julie McDowell:**

Thank you, Dr. Walk. To read Dr. Walk's article entitled Cancer Immunotherapy Biomarker Testing: what Pathologists Need to Know, please visit cap.org and enter "precision medicine" in the search function. Thank you for listening to this CAPcast. Be sure to listen to our other CAPcasts from the CAP on our SoundCloud channel by downloading the SoundCloud app on your mobile device. And we're also on Apple Podcast and the Stitcher app. To find this podcast, search for the word CAPcast on these apps. Once you find our podcast, be sure to click the subscribe button so you don't miss new CAPcast episodes.