# Diagnosing Advanced Colorectal Cancer - What Pathologists Need to Know

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**Julie McDowell:**

The advent of new molecularly targeted treatment strategies for patients with advanced colorectal cancer places anatomic and molecular pathologists as key players in the delivery of care for this large patient population. Specifically, advanced colorectal cancer encompasses patients presenting with stage four cancer or those who experience a cancer recurrence explains Dr. Joseph Willis in a new CAP article about testing of specimens from patients with advanced colorectal cancer.

Dr. Willis is vice chair for pathology translational research and a GI pathologist at Case Western Reserve University and University Hospital's Cleveland Medical Center in Ohio. In this role, Dr. Willis has pursued better understanding of pathogenesis and prediction of outcomes of patients with GI cancers. He also serves on the CAP's Personalized Health Care Committee.

Dr. Willis, in your article you discussed the multidimensional role the pathologist plays in determining treatment strategy, colorectal cancer. What has been your experience in your practice of pathology?

**Dr. Joseph Willis:**

I've been fortunate enough to be involved in the diagnosis, management and academic research discoveries in colorectal cancer for over 25 years. In that time, there's been an amazing improvement in multiple aspects of patient care starting from very basic issues such as standardizing lymph node dissection requirements all the way to the implementation of high-quality multidisciplinary tumor boards.

In tandem with that related to the really explosion of molecular data that has come on since the identification of the human genome and the Human Genome project, there has been an enormous increase in the understanding of the factors that govern the initiation and progression of colorectal cancers among many other cancers. And with that there's been an increased ability to use these new discoveries to manage patients. So with the marriage of both basic and translational and clinical research the standard of patient care has dramatically improved in that time.

**Julie McDowell:**

Now in your article, you state that mismatched repair testing using NGF platforms will likely see widespread adoption in the near future. What are some of the advantages of this approach?

**Dr. Joseph Willis:**

There are several advantages. Probably the single most important advantage. Is that many patients already will need next generation sequencing to highlight some of the molecular changes that might be useful in planning therapy for patients. So that means that these certain amount of tissue will be used to interrogate these molecular profiles anyway, so using that same tissue for an extra test will have many advantages.

Having said that, it's not necessarily a technology that will completely replace other modalities, especially immunohistochemistry because at least by current standards, NGF identification of microcellular unstable cancers are still not consistently able to identify the gene that has been dysregulated or mutated or undergone epigenetic silencing, which is done much better by immunohistochemistry.

There probably will be an increased use in this technology, but I don't think it will completely supersede the other technologies that we have here. Nonetheless, it is a very powerful tool and may over time be more sensitive to identify the false negative mismatch repair cases, which are only one or 2% by current technologies. And also finally, with molecular profiling, it may be possible to better predict different types of therapies in the future based on these mismatch repair profiles, although that still is a long way off.

**Julie McDowell:**

Speaking of therapies, you mentioned in your article the CTLA4 pathway for cancer therapy. In the context of evolving immunotherapies, what are the potential options for further uses of immunotherapy?

**Dr. Joseph Willis:**

There is an explosion of new data in this field in all aspects, in every cancer system. The incredible complexity that the immuno interface between cancers and immune cells has only really started. It's hard to imagine 10 years ago that this entire arm of therapeutics would even exist. I remember many years back in the eighties when people were trying to identify immunotherapy options for patients with melanoma with not much success. So this was really a great surprise.

Now the complexity of these systems are such that we're only beginning to scratch the surface. For example, there is a pathway in immunoregulation called Lag-3, and Lag-3 is very similar to the PDL1 pathway that's now being used to help patients with advanced cancers. When last I checked, there were 34 clinical trials in clinical trials.gov associated with potential Lag-3 immunotherapy in patients with colorectal cancer.

So it's possible that combining various methodologies in immunotherapies such as for example, PDL1, Lag-3, IDL1 in various cocktails dependent on identification of susceptibilities of patients will become a norm as time goes by as we get more data. So there is really quite a lot of work to be done even on the pathways that are now understood to be important, and it's very likely that this whole opportunity for immunotherapy will increase dramatically over time when basic and translational research programs develop new potential targets.

**Julie McDowell:**

What do you see as likely developments in treatment for RAS wild type cancer that resist targeted therapies?

**Dr. Joseph Willis:**

This is a big problem. Going back one step, we can say that even patients who have what we call extended RAS pathways that are found to be wild type, in other words, there are several genes in this pathway that we now currently assess, even those patients when treated and getting a response only have an approximate three-month extension of life, which is not very good.

That concept of these patients developing either resistance or not being susceptible to anti EGFR therapy to begin with are probably similar. And they probably are related to other factors in the EGFR pathway that effectively block the ability to inhibiting the EGFR receptor do not affect the metabolism of the cell. There are many potential genes such as PIK3CA, P10, AKT, even the JAK/STAT pathway, all of which might need to be investigated going forward in all patients who have stage four colon cancer and are at the end of standard therapy and are potential candidates for EGFR therapy.

With that in mind, it's likely that extensive molecular testing will be needed to identify what patients will in actual effect have their susceptibility to EGFR therapy confirmed.

Another important aspect about the development to resistance of anti EGFR therapy is the concept that resistance occurs most likely based on the fact that sub clones in the cancers become prominent after chemotherapy kills off cancer cells that are susceptible to certain types of therapies. In order to make sure that patients are not treated with therapies after their cancers become resistance it's important to identify, if at all possible when this switch occurs.

Currently, technologies such as circulating tumor DNA, where the so-called liquid biopsy technology allows next generation sequencing to pick up circulating mutations from cancers that are a signal that the patient's cancer has become resistant to therapy, is an important emerging technology and will very clearly become standard of care in the not too distant future.

**Julie McDowell:**

Finally, Dr. Willis, what do you see as the next big issue to address in advanced colorectal cancer diagnosis and treatment?

**Dr. Joseph Willis:**

Going forward there are multiple fronts that need to be attacked in order to make consistent improvements in outcomes of patients with metastatic colorectal cancer. One of the most important is highlighted in a recent paper from the personalized health committee of the CAP identifies specimen handling prior to a receipt in the pathology department and also the way the specimens are handled in the pathology department as being vital in order to ensure the subsequent accuracy of any sophisticated testing that will be done on those cases. We have recognized that already, for example, in how we handle breast cancer specimens but going forward, this will probably be true for all cancer specimens. Also, just adherence to standard processes such as adequate lymph node dissections in patients with early stage cancer to make sure that we're not missing a stage three cancer and calling them a stage two. That's really very important.

But in reality, we also need new therapies. We badly need new therapies to help these patients because as I said previously, the anti EGFR therapies, which are our best personalized medicine in metastatic colon cancer only on average extend light expectancy by about three months in patients who have KRAS wild type cancers. With that and vitally important is the need to develop good biomarkers. There has been a recognition in multiple institutions involved in cancer research and cancer care that without good biomarkers, we may not identify patients who would benefit from therapies and as importantly, avoid giving therapies to patients for whom the drugs will not do any good and thereby, for example, not availing them of different opportunities of patient care.

Also, there are many other aspects that we go on for a long time, but for example, there are novel tools arising in anatomic pathologies such as whole slide imaging with deep learning capabilities that may in actual fact be useful as surrogate signals for prognosis and predictive values going forward. And that's only in its early stage, but the likelihood is that will become an important part of a patient cancer record. Also, we need to be better at data integration overall. It's not just pathology. Remember, this is a holistic view of patient care that we have to include and for example, it was identified that right-sided colon cancers, even though they're extended RAS wild type, have a different response to anti EGFR therapy and those sort of holistic components of patient clinical and pathologic features need to be incorporated in final reports.

There are also other things that pathologists are at the forefront of, and then things that have to be highlighted are things such as cost containment. Even though we have and are developing extensive new tools to be able to identify patients who might be at high risk of cancer recurrence and thereby shepherding them to different therapies, if these tests become unavailable to the vast majority of people because of cost and they are useless. So we have to make sure that we work very hard at test utilization and cost containment to make these tests available to everybody.

And I guess finally, it's very important for us to be cognizant of pathologists, that we really have this major role of data integration. Clinicians really look to a pathologist to be able to put all the different aspects of a cancer workup together in one succinct report so that then they can readily identify the options that are available for patients. And it's up to us to make sure that we have the knowledge base to do that, plus the clinical informatics programs that allow the delivery of care, and also to be in constant conversation with our clinical colleagues to make sure that the systems that we put in place are effective.

**Julie McDowell:**

Thank you, Dr. Willis. Dr. Willis's article is entitled Testing of Specimens from Patients with Advanced Colorectal Carcinoma, which can be found in the precision medicine section of cap.org. Please visit the website and enter precision medicine in the search function to locate this article as well as others.

The CAP'S Personalized Health Care Committee curates this page, which offers links to scholarly articles and presentations on precision medicine topics such as PDL1 or the use of liquid biopsies. In addition to these public resources, the page also lists some resources accessible by CAP members. These include the short presentations on emerging concepts and the precision medicine resource guide.

Of course, there are also links for visitors to the Resource Center to contact committee members for more information or to lead feedback. It's important to note that precision medicine is a rapidly evolving field, and the Personalized Health Care Committee launched this resource center via central location for current information on precision medicine. As a result, its content will change and be updated regularly. The committee encourages visitors to return regularly to see what's new.

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