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Precision Medicine in NSCLC

Implications for Molecular Testing and Treatment

This transcript has been edited for style and clarity and includes all slides from the presentation.

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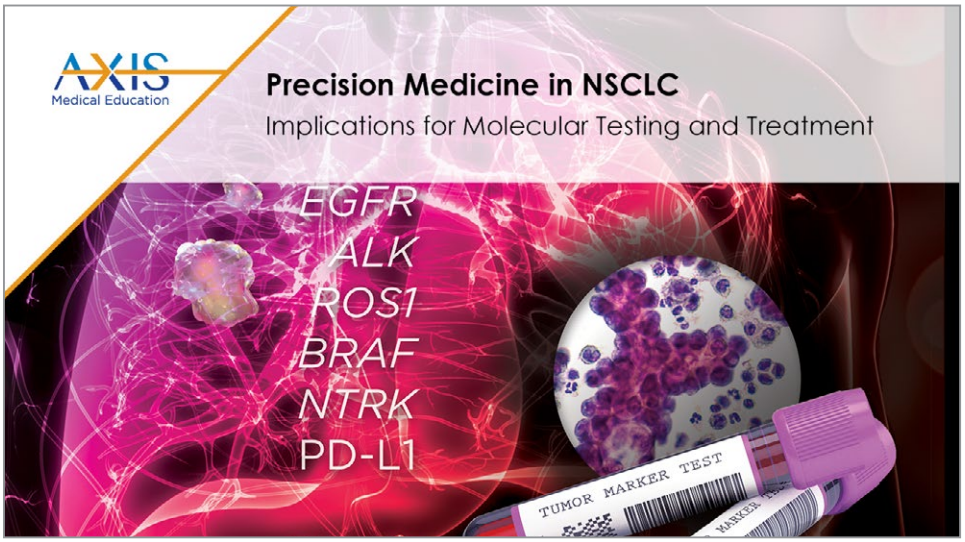
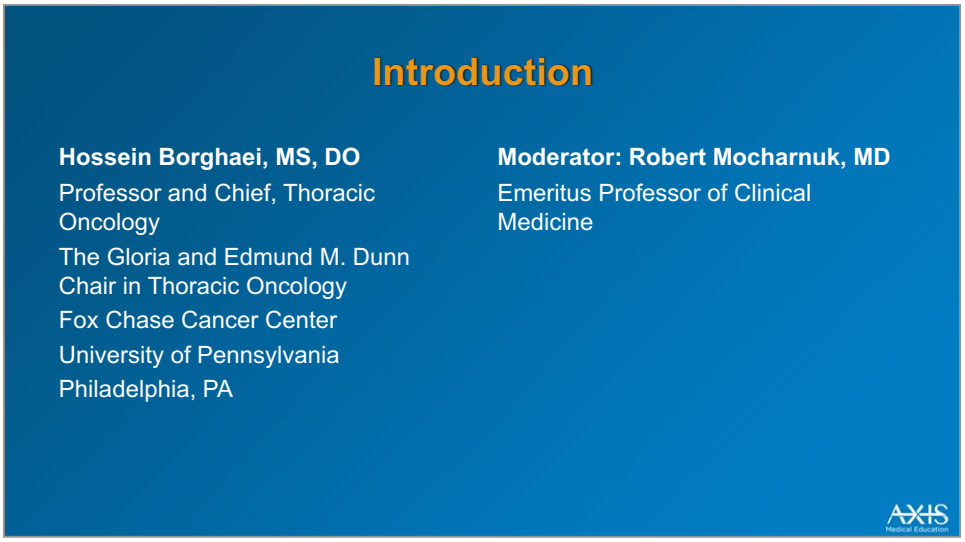
Precision Medicine in NSCLC: Implications for Molecular Testing and Treatment

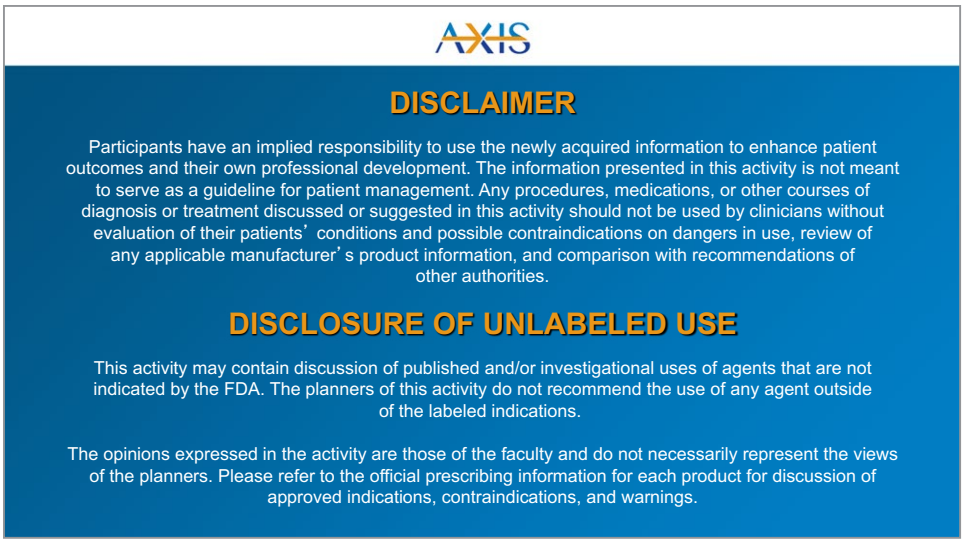
Hossein Borghaei, MS, DO



Robert Mocharnuk, MD: Hello, and welcome to part one of this educational activity entitled *Precision Medicine in Non–Small Cell Lung Cancer: Implications for Molecular Testing and Treatment.*



I am Dr. Robert Mocharnuk, Emeritus Professor of Clinical Medicine, and I am joined today by Dr. Hossein Borghaei, Professor and Chief of Thoracic Oncology at the Fox Chase Cancer Center in Philadelphia, Pennsylvania.



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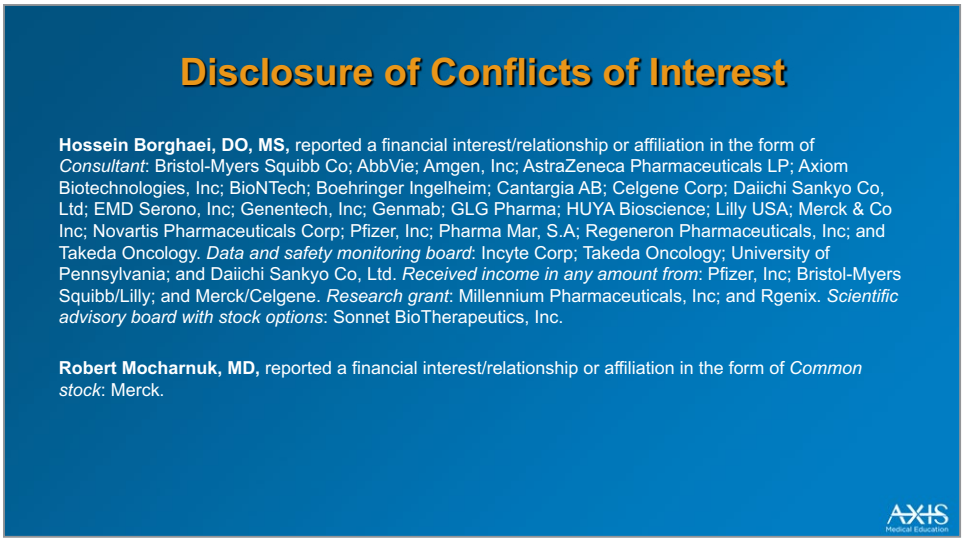

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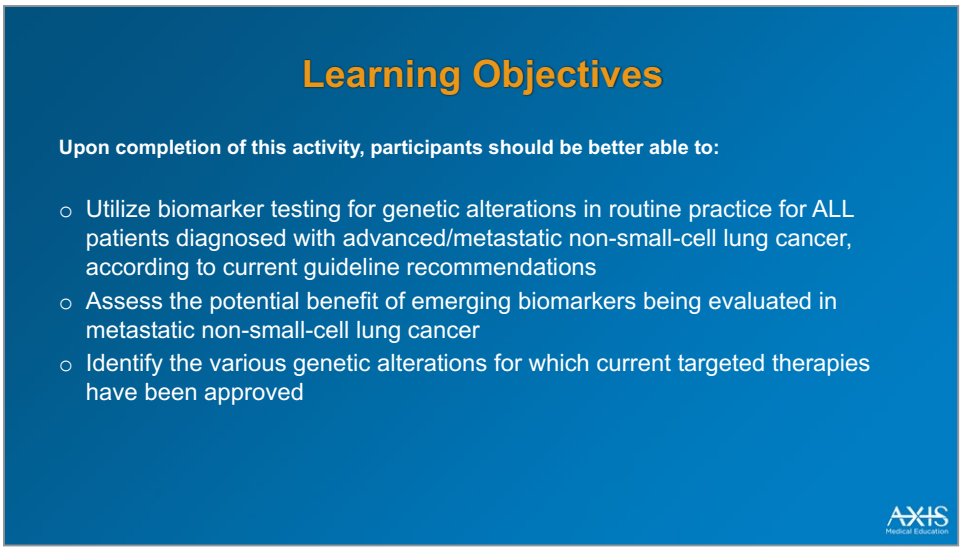
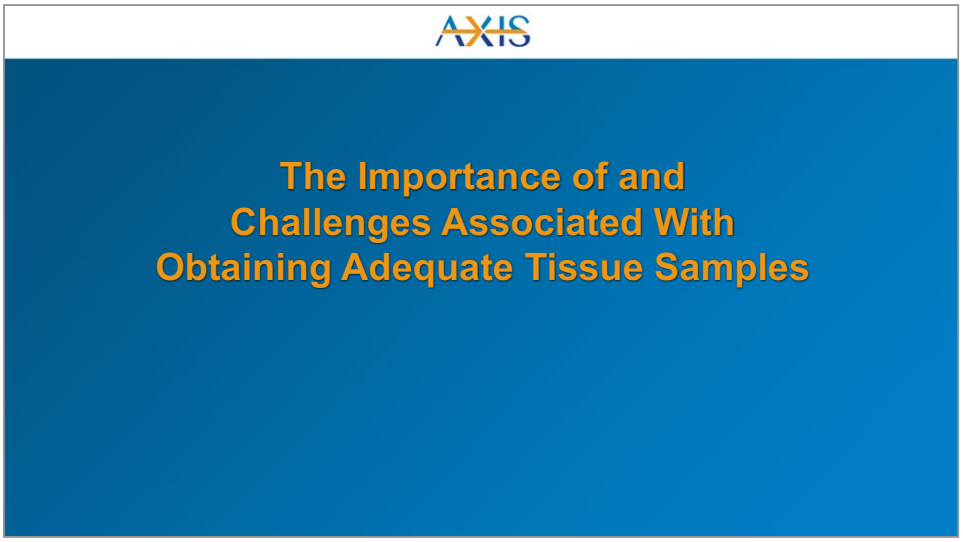
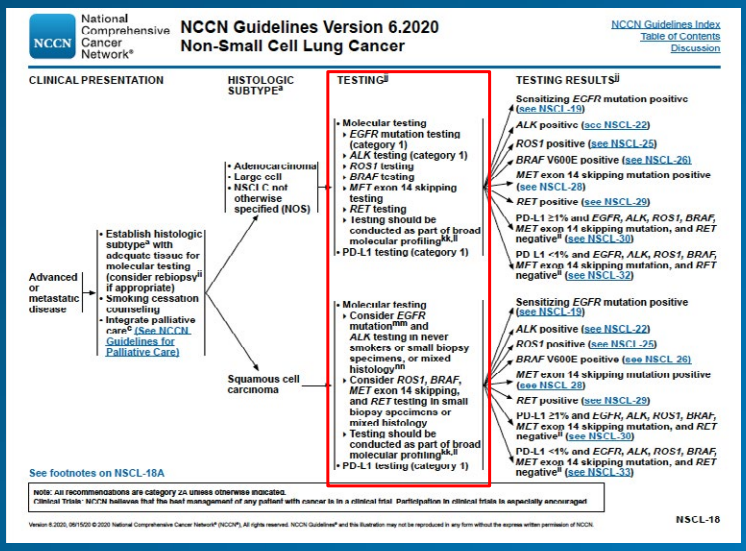


- Here are the learning objectives for this activity. Today in part 1 of this activity, we will review and evaluate the most recent data and recommendations and provide expert insights on biomarker testing for genetic alterations in non–small cell lung cancer. We hope that you'll join us for part 2, where we will review currently available targeted therapies for the treatment of advanced non–small cell lung cancer based on the presence of identified mutations and gene arrangements that we will discuss today.



- Let's start by discussing the importance of and challenges associated with obtaining adequate tissue samples for biomarker testing in advanced or metastatic non–small cell lung cancer patients. First, Dr. Borghaei, would you review current recommendations concerning which gene mutations, rearrangements, and fusions we should be testing for in our non–small cell lung cancer patients?

Current NCCN Guidelines® Testing Recommendations Includes Testing for Many Gene Mutations



- Recommend testing for:
  - *EGFR*
  - *ALK*
  - *ROS1*
  - *BRAF V600E*
  - *MET* exon 14
  - *RET*
  - PD-L1
- In addition, testing is also recommended for evolving biomarkers such as high-level MET amplification, *HER2, NTRK,* and TMB

PD-L1, programmed cell death protein ligand 1;TMB, tumor mutational burden.
Velcheti and Pennell. *Ann Transl Med*. 2017;5(18):378.

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Hossein Borghaei, MS, DO: Thank you for inviting me for this program, and thank you for that question. The easiest way to answer this particular question is to look at this page from the NCCN Guidelines®. It is important to realize that the list of alterations, mutations, translocations, and all other genomic alterations is actually increasing. We now have 7 to 8 different molecular markers that we can target. And there are at least 7 FDA-approved treatments for patients with various molecular alterations.

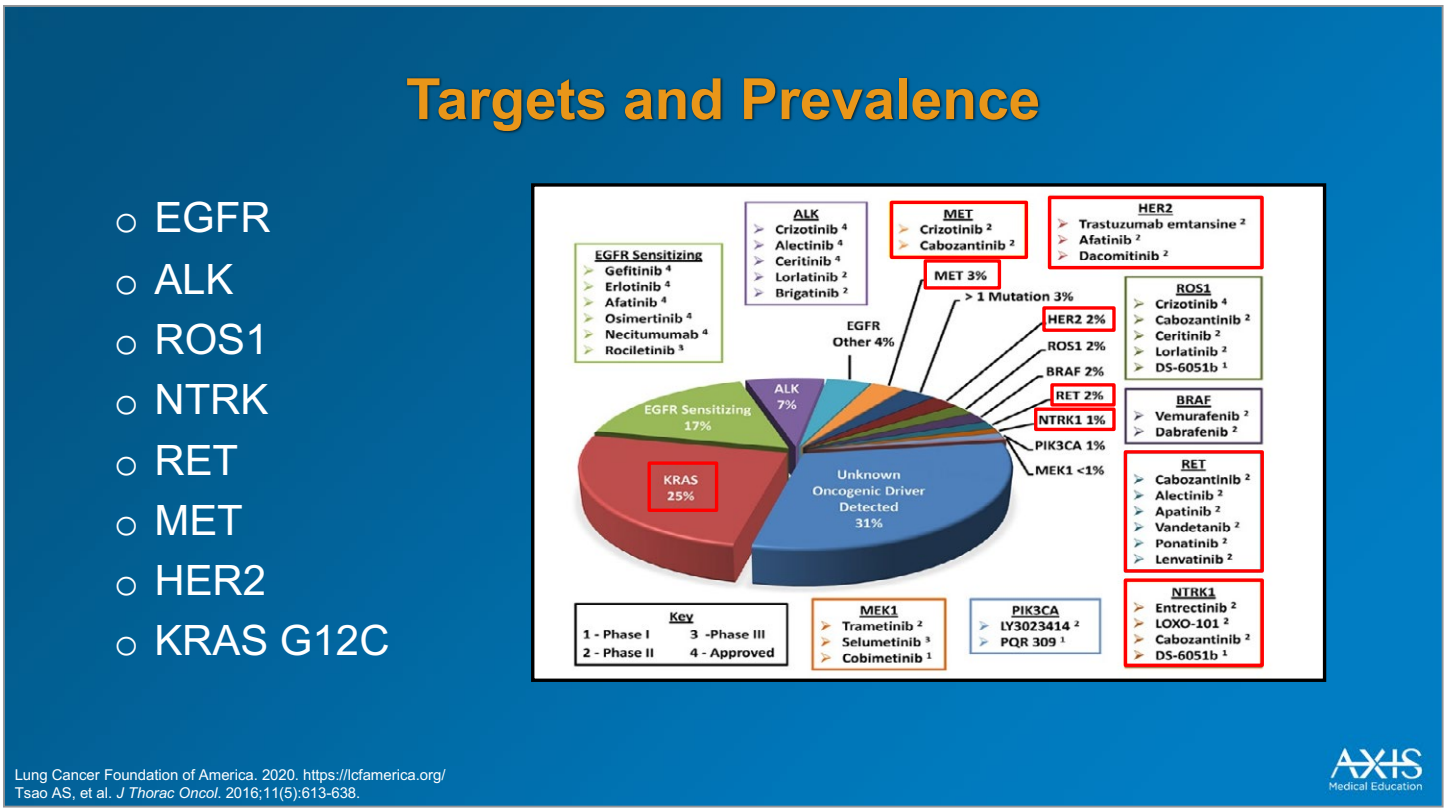
What is important to realize is that we have come to a point where practically every patient who has advanced non–small cell lung cancer, particularly nonsquamous histology, should have a broad next-generation sequencing platform done as part of their initial workup. The way I look at this is that this information is as important as having staging information because you want to decide how to best treat this particular patient. Therefore, it is important to have this information.

It is also important to realize that doing these one-off testings that we used to do is no longer feasible because the number of changes that we're looking for, as we can see on this particular slide from the NCCN Guidelines, is increasing. It is no longer cost effective. In addition, it is not possible to have adequate tissue to perform one test at a time.

To have tissue stewardship and to have the best treatment options for all of our patients with advanced non–small cell lung cancer, the best option now is to perform a comprehensive next-generation sequencing on every patient who walks through the door. We can debate a little bit about squamous histology. I would say that in my clinic, if I have someone who is a never smoker, who has squamous cell histology, I would seriously consider doing all of the testing.

We can discuss the impact of tissue testing and blood testing as part of this workup. Later on in the program, we will review some of the data. But the bottom line is that if you do not look for these alterations, you're not going to be able to find the patients. And therefore, you might not offer the best treatment option to your patients.

Dr. Mocharnuk: Knowing what we should be testing for, what is the prevalence of these mutations, rearrangements, and fusions in non–small cell lung cancer, and the rationale for targeting them in non–small cell lung cancer?

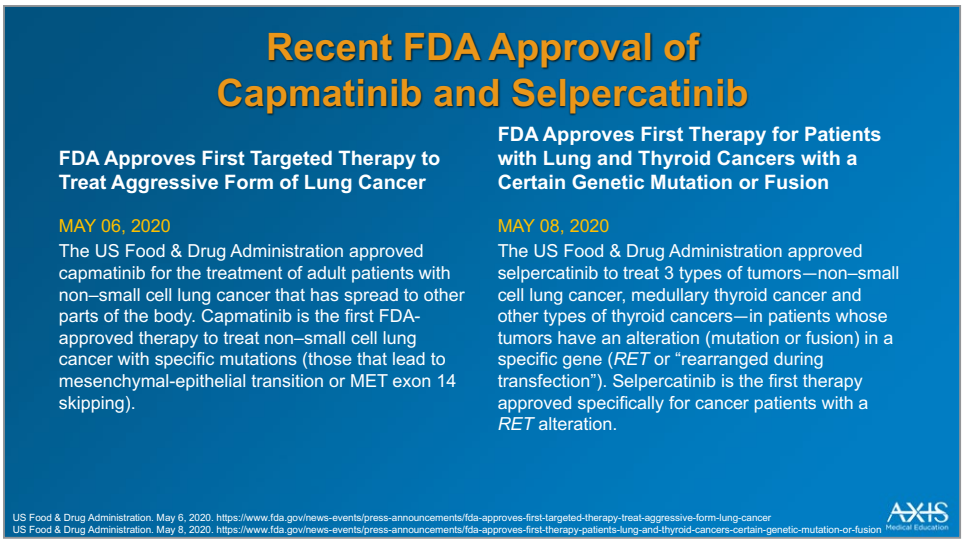


Dr. Borghaei: Some of these mutations and some of these alterations are extremely rare, meaning that you can find them in 1% to 2% of all the patients that you see with the diagnosis of non–small cell lung cancer. Some of the numbers that you see on slides like this indicate that even the prevalence is low because we have really effective treatment options, such as of a simple pill that some patients can take.

It is important to identify these patients, and it is important to offer them the right treatment. Some of the highlighted pathways and molecular alterations in this particular slide are there to indicate that even though we're dealing with rare phenomena—for instance, in the setting of a *RET* fusion or some of the *NTRK* alterations—you're talking about 1% to 2% of patients who could possibly have this. But we have multiple really effective drugs. Some of these drugs offer intracranial responses, which is amazing, thinking about caring for a patient with non–small cell lung cancer with brain metastases, and how important it is to have the right drug in the right patient because it could have an impact in the overall outcome of the care that we deliver.

And the alterations that we're showing on the left-hand of the slide, *EGFR, ALK*, those are obviously the more well-known ones, all the way down to *KRAS* G12C and *HER2*. These are alterations that we're aware of. We can find them if we perform next-generation sequencing, which is a comprehensive genomic analysis. And even though we don't have approved drugs right now for *HER2* or *KRAS* G12C, there are multiple studies looking at what may be effective therapies right now.

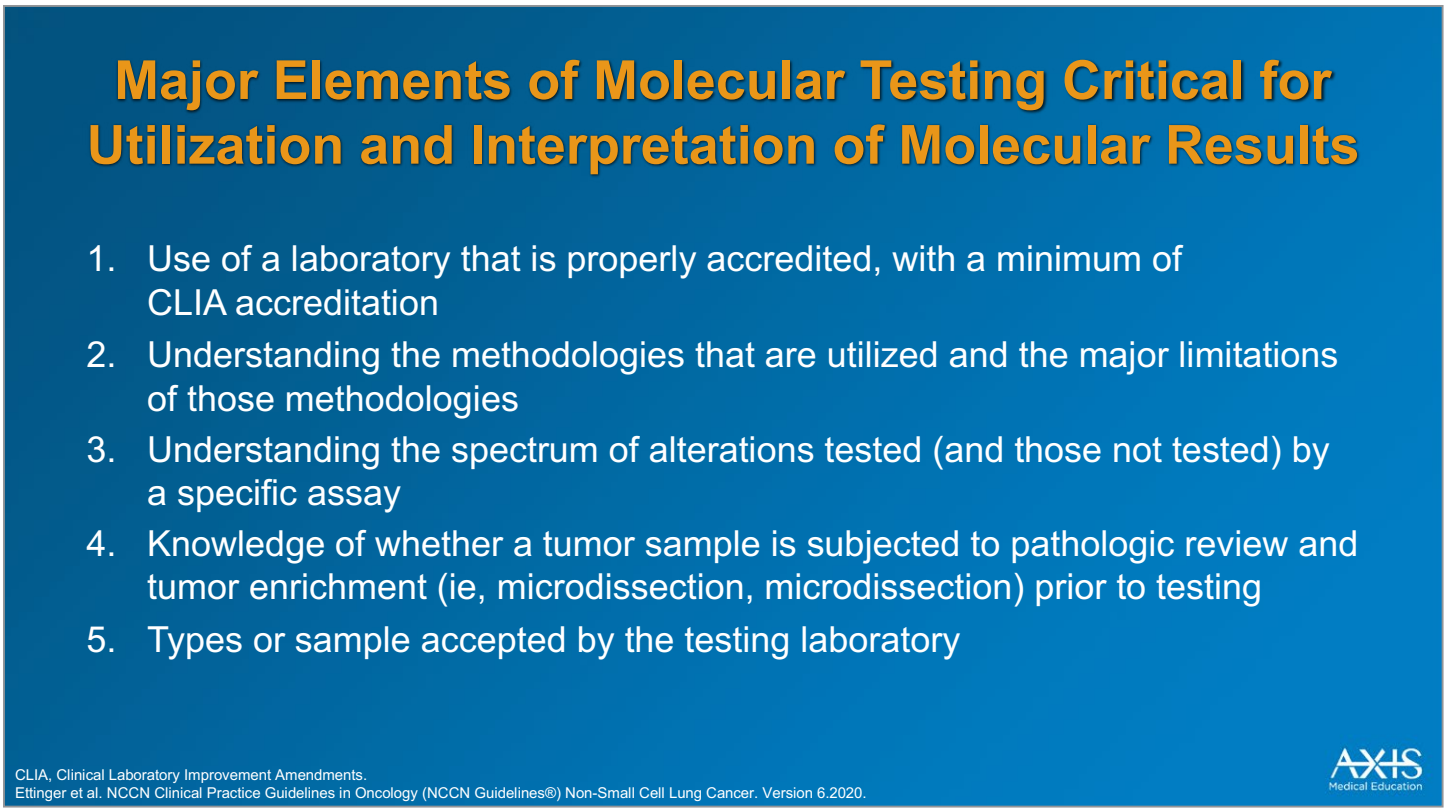
So the key here is to identify these patients, and to be able to say that you have these alterations to identify, so that when a drug becomes available, you can offer it to patients who qualify for it.



- The list is expanding. These are just 2 examples from early May—the FDA approved drugs for *MET* alterations and *RET* alterations. These represent major breakthroughs for management of patients with non–small cell lung cancer. I know it's a repeat of what I have just said, but unless testing is done in every patient who comes in, we are going to miss these patients.

  You do have to screen a large number of patients to find some of these more rare alterations, mutations, fusions. But it is worth it, and it will have an impact on a patient's outcome.

- **Dr. Mocharnuk:** Dr. Borghaei, how can clinicians identify these biomarkers in patients with non–small cell lung cancer?



Dr. Borghaei: That's a really good question, and it's an important one. There are a number of different pathways that one can take to identify the patients who would qualify for these specific treatments. Obviously, obtaining adequate tissue from somebody who has a diagnosis of lung cancer is always difficult unless they have more accessible sites where we can safely and easily perform a biopsy.

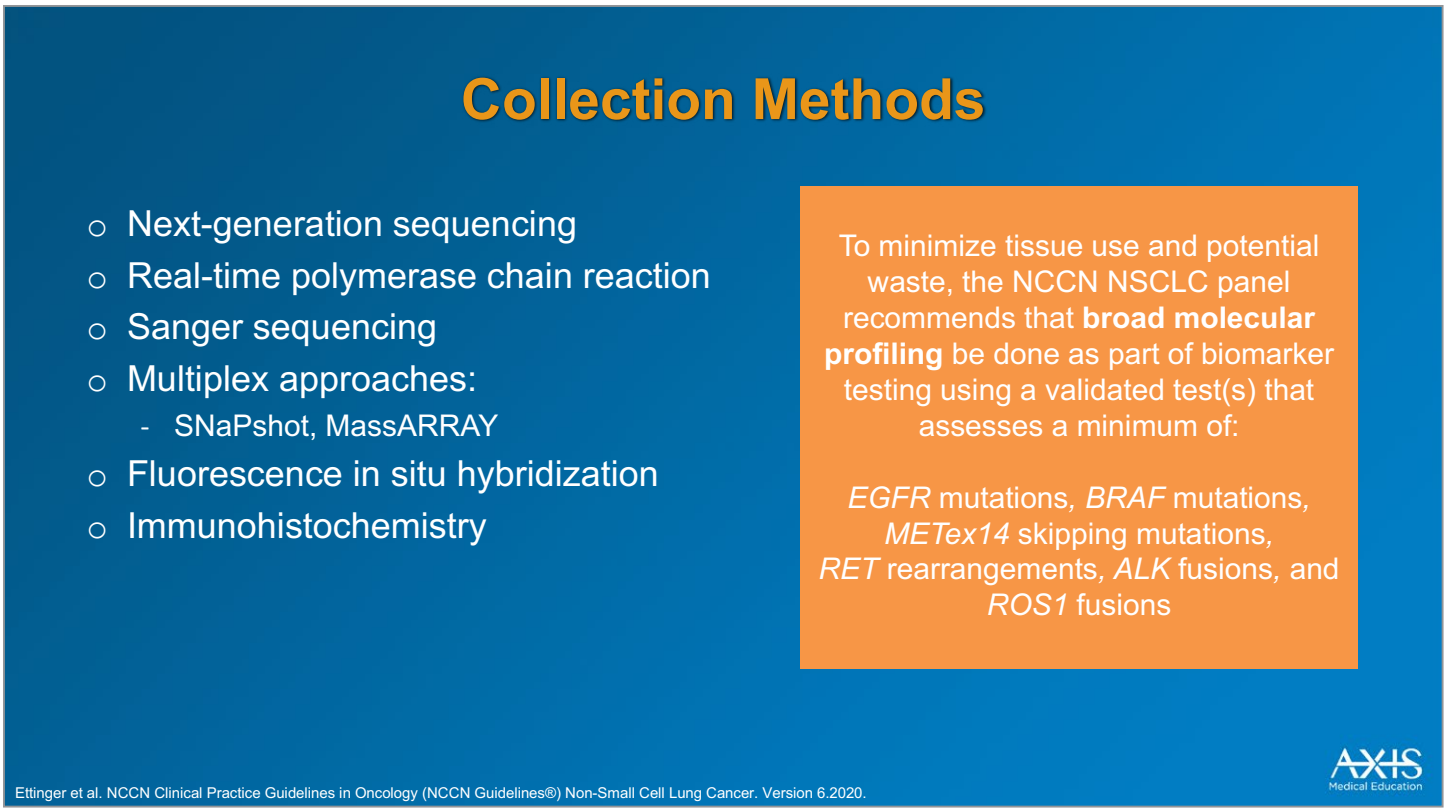
It is important to have a team approach to all of this. It is important for interventional radiologists or whoever performs the biopsies at your institution—everyone who touches a tissue to be aware of the importance of having enough samples collected and preserved for all the testing that we need to do.

In some centers, like my center, we have an in-house comprehensive panel performed on all of our patients. Sometimes you have to obtain the tissue and send it out. So it's important to know where you're sending it to and what it is you're asking for.

So you want to use a laboratory that's properly accredited and also properly trained. You don't want the tissue to be wasted. It's important to be aware of the methodologies used. If you simply send something for mutational analysis, you're going to miss all the fusions and all the potentially good drugs that we have under that category. So it is important to communicate with the laboratory, perhaps with your pathologist, to say hey, this is the list of alterations that we absolutely need to know about to take care of a patient. So, understanding what it is that you want to do with the tissue is important.

Sometimes pathologists have a tendency to perform a lot of immunohistochemistry (IHC) studies to identify subtypes of lung cancer. And that's appropriate in some cases. However, in some cases, maybe 1 or 2 tests would be enough. This way, you've preserved the rest of the tissue for all the molecular and other testing that's required to determine treatment options for the patient.

There is a lot for the medical oncologists to be aware of. However, because it is a medical oncologist who is in charge of the care of the patients, it is also appropriate for the medical oncologists to have that open interaction with everyone who touches the tissue to ensure that the appropriate care is delivered.



▶ What are some of the methods that we use? We talked a lot about next-generation sequencing. That's probably one of the more common ways of doing things now because it is more cost effective, it requires less tissue. Polymerase chain reaction is used from time to time. Sanger sequencing is a little outdated in a sense that we don't want to do single-gene alterations. We want to be able to do a more comprehensive, more in-depth analysis of all the tissue that we have available to us.

There are some alterations for which we still use fluorescence in situ hybridization to identify. You have to notify your pathologist and the lab that you work with what you're looking for. Of course, we still do a lot of IHC tests—some for diagnosis and for certain biomarkers such as programmed cell death protein ligand 1 (PD-L1); it's less expensive, it's quicker, and it can be incorporated a lot more easily into the workup of a tumor sample that's delivered to the pathology department.

It's not as complicated as a molecular test requiring specialized laboratories, but it has limited use right now.

So PD-L1 is basically the one that we use. Perhaps you can use IHC for *ALK* identification. But beyond that, you still rely on next-generation sequencing to find all of the mutations that we are basically looking for, for our patients, so there's more information on this slide.

Commercially Available Biomarker Assays

Diagnostic Name	NSCLC Indication(s)
***therascreen* EGFR RGQ PCR Kit**	gefitinib, afatinib, dacomitinib
cobas EGFR Mutation Test v2	erlotinib, osimertinib, gefitinib
PD-L1 IHC 22C3 pharmDx	pembrolizumab
FoundationOne CDx	afatinib, gefitinib, erlotinib, osimertinib, alectinib, crizotinib, ceritinib, dabrafenib, trametinib, capmatinib
VENTANA ALK (D5F3) CDx Assay	ceritinib, crizotinib, alectinib
Oncomine Dx Target Test	dabrafenib, trametinib, crizotinib, gefitinib
Vysis ALK Break Apart FISH Probe Kit	crizotinib, brigatinib
VENTANA PD-L1 (SP142) Assay	atezolizumab
PD-L1 IHC 28-8 pharmDx	nivolumab + ipilimumab

NSCLC, non–small cell lung cancer.
https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools.

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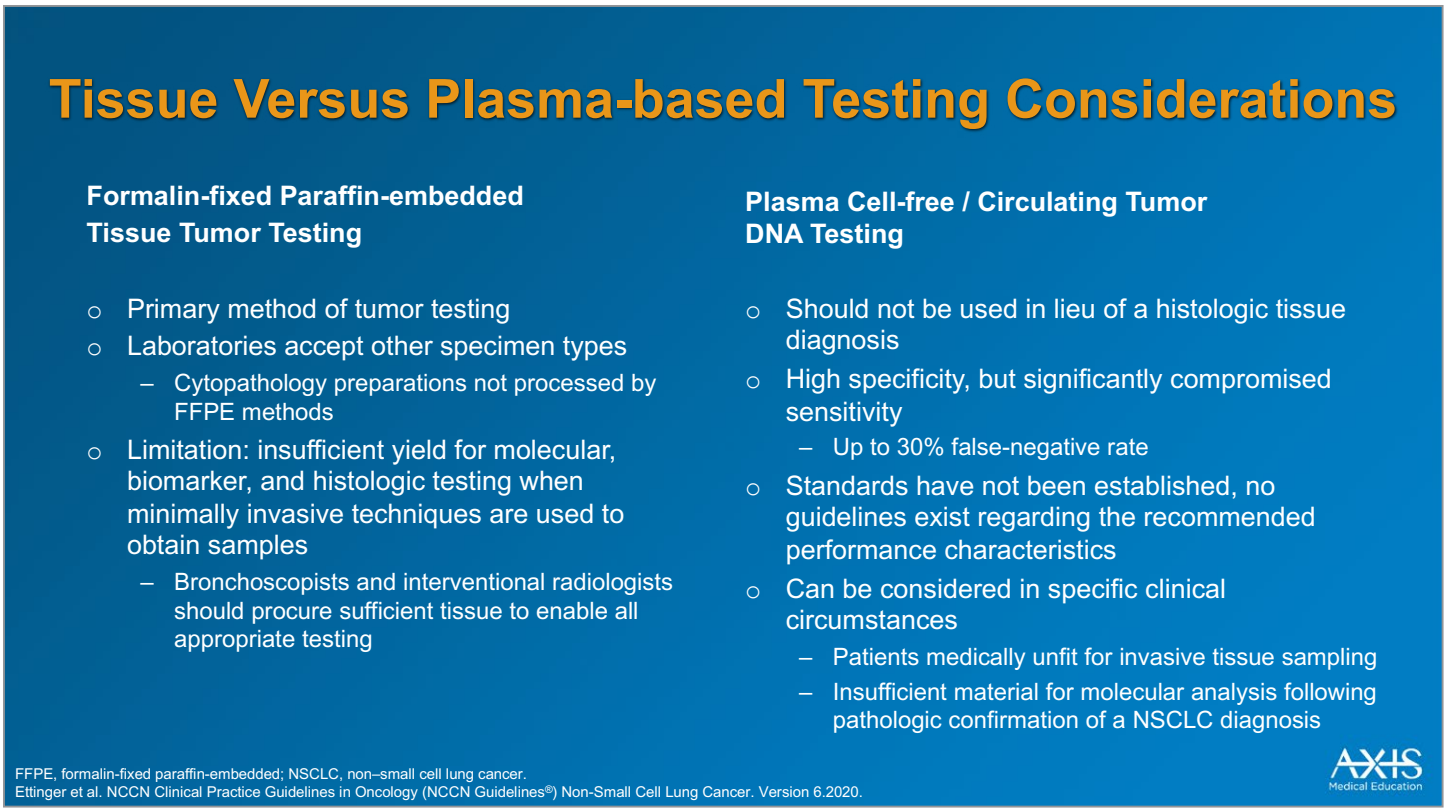
When you read a piece of literature or a manuscript, you might see any number of techniques used, and some of them aren't shown on this particular slide. To summarize, some of these tests are used to identify single alterations. For instance, if you use the first one, therascreen EGFR, and you're only looking for *EGFR*. If you use the Ventana ALK Assay, you're looking specifically for *ALK*.

If you use a more broad type of next-generation sequencing, you can get all of the potential mutations that could be there. I'm talking about *EGFR* mutations, *KRAS*, or any number of other mutations that might be detected. Using PD-L1 with a specific company, for instance, will give you just a PD-L1. And you need that to tailor your treatment for the particular patient. But that doesn't give you *EGFR, ALK, BRAF, HER2*, or all the other alterations that may be in the tumor.

Knowing what test you are requesting is important. To some extent, some of what we're showing in this slide, it's a little bit outdated, but not quite as useful as we want it to be, given the present status of having to find 7 or 8 different markers.



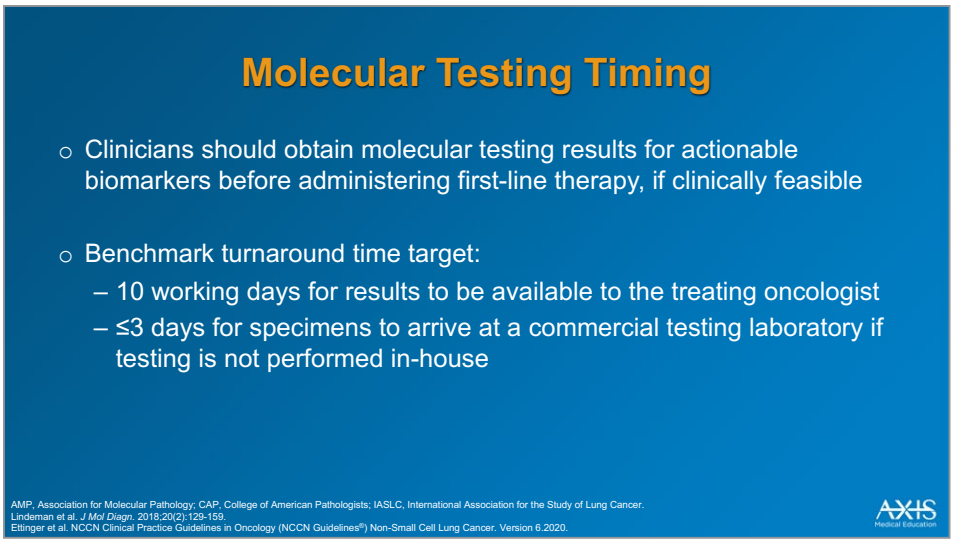
What about liquid biopsy? It's a great idea. It is potentially the future of doing all of these analyses. Why? Because we all realize it is difficult to obtain adequate tissue. Again, if you're dealing with a patient with lung cancer, and the only sites of disease are lungs and lymph nodes, it is not easy to have access to a big chunk of tissue, to do all the testing that you need to do.

Tissue is probably more specific. I would still say that it is "the gold standard," but plasma testing can augment what you do with tissue, and there are data for that. And in certain cases where you just cannot get adequate tissue, plasma testing can provide a lot of useful information. Yes, there is a false-negative test, meaning that the sensitivity of the test is a little bit low. So if your plasma testing is completely negative, you cannot be 100% sure that that particular patient does not have any mutations. You still need tissue to confirm it.

However, in cases where you simply cannot have access to adequate tissue, sending plasma for testing can actually solve a lot of problems. What if you do find *EGFR*? Then you're on your way. The patient can get appropriate treatment, and you can proceed from there.

Plasma testing can augment tissue testing. There are a number of reports saying that tissue can have a false-negative test result, plasma can have false negative. But if you put the two of them together, you can actually identify more patients with these genomic alterations. I understand that cost becomes an issue, and everybody talks about how expensive some of these tests are. But when you think about the care of a patient with metastatic non–small cell lung cancer and how much more we can offer, cost really becomes a little bit less important. Identifying patients who can get these directed therapies becomes even more important as far as I'm concerned. There's a lot of debate about that.

So, there is a convenience for plasma testing, but it's less sensitive. There is a little bit more difficulty in obtaining tissue, but it's worth the effort at the time of initial diagnosis, and perhaps even at the time of progression, as we get to talk about certain scenarios. But the bottom line is that we have to make every effort possible to identify these patients.



We think these actionable alterations or mutations can have an impact on how we care for these patients. The problem is that if you're relying on tissue, it takes a long time to get the results back. That's a valid criticism of some of the testing. But molecular testing has been around for a long time.

There are a number of national and international guidelines that provide benchmarks for when we should be able to get the molecular results. If you work with the laboratory, if you work with your pathology department if this is really an interdisciplinary approach, a lot of these things can be streamlined. For instance, 10 working days to get the results from the moment the sample is sent is a very reasonable turnaround time. Sometimes it takes that long to get all the staging material done, or studies done for a patient.

It's important to keep that in mind. There are instances where, by the time you obtain adequate tissue, send it to your pathologist, from your pathologist sending it out, from sending it out, delivering to the appropriate institution or facility where they do the testing to get the results, might be 3 to 4 weeks. That, obviously, is not acceptable. So you need to come up with a process where things are streamlined to the extent that if your system allows it, to get these results within 10, 12 days. So patient care is not delayed and you get the information that you require.

I see patients in the clinic, perhaps not as much as some of you in the clinic at this point, but I still see patients 2 days a week. It's anxiety-inducing for a patient and for a physician to say, you have potentially stage IV non–small cell lung cancer, but I'm not going to treat you because I'm waiting for more information. And I can understand how a patient might come back and say, well, I'm not willing to wait. I need to get started.

That's where having an open dialogue with the patient and making sure all the information is communicated with the patient and family is important. Continue to follow the patient closely but get the data to deliver that personalized level of care that a patient requires.

Dr. Mocharnuk: Dr. Borghaei, what methodologies and assays do you use most often in your practice? Have you ever had a patient with insufficient tissue to perform appropriate molecular analysis? Is this an instance where you would rely on plasma cell-free/circulating tumor DNA testing?

Dr. Borghaei: Right, so have I had patients where we've had inadequate tissue? Of course. It happens. It's a clinical practice. So if I really get a sense that a patient is in trouble, meaning that the disease is progressing rapidly, I still try to perform a biopsy as fast as I can. But then, in scenarios like that, I am more inclined to start just a platinum doublet chemotherapy just to stabilize everything, and then wait for the molecular testing to come. But I do perform that second biopsy.

I am now incorporating liquid biopsy into my practice a lot more. I have to admit, I am a recent converter to this. I always believed that tissue should be sort of the sample sent for molecular testing. But the improvement in the liquid biopsy panels, some of the fantastic data that has come out recently has really pointed to the fact that for some patients, getting that liquid biopsy panel sent is really important. The results come back a little bit faster.

If results are negative, I still have the tissue, which is being sent out or being worked on. So I obtain the molecular testing results at all costs.

Dr. Mocharnuk: Thank you for that insight. Now let's turn to guidelines for molecular testing. The College of American Pathologists, International Association for the Study of Lung Cancer, and the Association for Molecular Pathology last released guidelines in 2018. Would you briefly review these recommendations?

2018 CAP/IASLC/AMP Molecular Testing Guideline

Reaffirmed and Updated 2013 Recommendations
Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection
Pathologists and laboratories should not use *EGFR* copy number analysis (ie, FISH or CISH) to select patients for EGFR-targeted TKI therapy
Molecular testing of tumors at diagnosis from patients presenting with early stage disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its multidisciplinary oncology team
Physicians must use *EGFR* and *ALK* molecular testing for lung adenocarcinoma patients at the time of diagnosis for patients presenting with advanced stage disease or at progression in patients who originally presented with lower stage disease but were not previously tested
Pathologists may use either cell blocks or other cytologic preparations as suitable specimens for lung cancer biomarker molecular testing
Laboratories should use, or have available at an external reference laboratory, clinical lung cancer biomarker molecular testing assays that are able to detect molecular alterations in specimens with as little as 20% cancer cells
Laboratories should not use total EGFR expression by IHC testing to select patients for EGFR-targeted TKI therapy
Laboratories should not use *EGFR* mutation-specific IHC testing to select patients for EGFR-targeted TKI therapy

AMP, Association for Molecular Pathology; CAP, College of American Pathologists; CISH, chromogenic in situ hybridization; FISH, fluorescence in situ hybridization; ASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; TKI, tyrosine kinase inhibitor.
Lindeman et al. *J Mol Diagn.* 2018;20(2):129-159.

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Dr. Borghaei: What you see on your screen is the College of Pathologists' recommendation for molecular testing. Some of these have been around for many years. And again, it emphasizes what we have discussed up to now. It is important to have the testing. It is important to identify the patients because then you can direct your therapy a lot more accurately than it would be otherwise, meaning the days that we would just give chemotherapy to everybody who walked in are gone. We have to identify the right patients for the right treatment, and these guideline recommendations help.

The other thing that the guidelines emphasize is this close collaboration among the pathologists, the treating physicians, and the person who performs the biopsies. This ensures tissue stewardship and that everybody's on the same page as to what has been requested from the pathologist or from the molecular pathologist, or if you're sending it out, from the molecular lab where you're sending all of this.

2018 CAP/IASLC/AMP Molecular Testing Guideline (cont.)

Summary of 2018 Guideline Statements	
What methods should be used to perform molecular testing?	IHC is an equivalent alternative to FISH for *ALK* testing
	Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, and *ROS1*
	Laboratories should ensure test results that are unexpected, discordant, equivocal, or otherwise of low confidence are confirmed or resolved using an alternative method or sample
Is molecular testing appropriate for lung cancers that do not have an adenocarcinoma component?	Physicians may use molecular biomarker testing in tumors with histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver
What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?	In lung adenocarcinoma patients who harbor sensitizing *EGFR* mutations and have progressed after treatment with an EGFR-targeted TKI, physicians must use *EGFR* T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy
	Laboratories testing for *EGFR* T790M mutation in patients with secondary clinical resistance to EGFR targeted kinase inhibitors should deploy assays capable of detecting *EGFR* T790M mutations in as little as 5% of viable cells
	Currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for lung adenocarcinoma patients with sensitizing *ALK* mutations who have progressed after treatment with an ALK-targeted TKI
What is the role of testing for circulating cell-free DNA for lung cancer patients?	Currently insufficient evidence to support the use of circulating cell-free plasma DNA molecular methods for the diagnosis of primary lung adenocarcinoma
	In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA assay to identify *EGFR* mutations
	Physicians may use cell-free plasma DNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative
	Currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of *EGFR* or other mutations, or the identification of *EGFR* T790M mutations at the time of EGFR TKI resistance

AMP, Association for Molecular Pathology; CAP, College of American Pathologists; FISH, fluorescence in situ hybridization; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; TKI, tyrosine kinase inhibitor.
Lindeman et al. *J Mol Diagn*. 2018;20(2):129-159.

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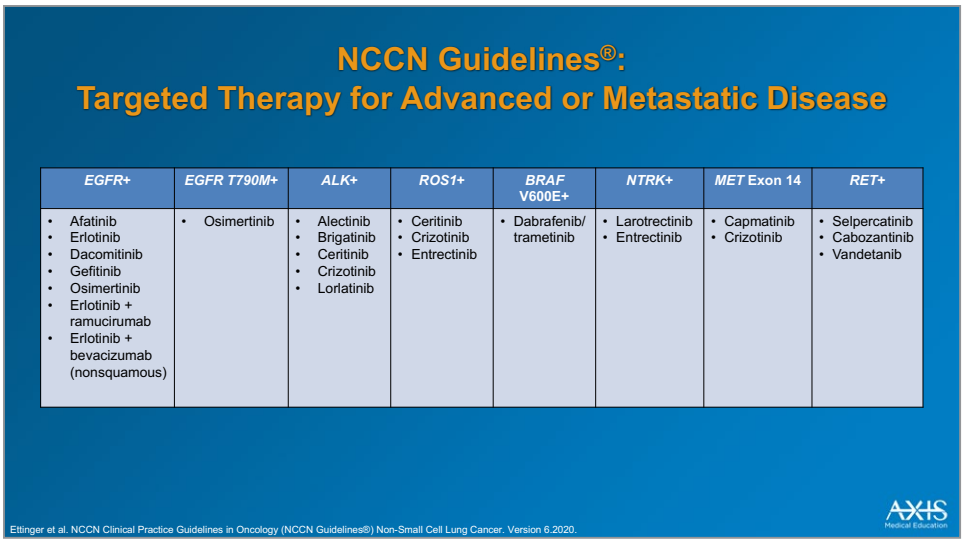
This is a summary of what we have talked about for the most part. Clinical practice is fast moving. The data that's coming in is fast moving. The data are really good for these targeted therapies. We owe it to the patients and to ourselves to do the best job that we can to care for the patients who are facing incurable diseases.

We talk about the metastatic setting and stage IV, but with some of the recent data coming out, I would not be surprised if we see molecular testing moving even to the frontline, in the adjuvant setting. Really good data were presented at this year's ASCO virtual meeting. Some of the studies that have been presented recently could have an impact on how we care for these patients, even in the adjuvant setting.

So now, molecular testing is going to move even to an earlier stage of treatment. And therefore, being aware of all of these points that we have discussed and all the guidelines that have been discussed and shown is really important.

Dr. Mocharnuk: We will discuss targeted therapies in more depth in part 2 of this activity. But for now, would you briefly review available targeted therapies for the treatment of advanced or metastatic non–small cell lung cancer, based upon biomarker analysis results?



Dr. Borghaei: Right, in the second part of the program, I hope to get a chance to cover some of the data for the specific alterations and drugs that you see. *EGFR* has been around for a long time. We know a lot about some of the drugs that are available in this setting. We know about T790M, less of a problem now because we're using osimertinib in the first-line setting. Drugs for *ALK, ROS1, BRAF, NTRK, MET,* and *RET* are all the additions that have come in a more recent time. *MET* and *RET* are brand new, as we discussed earlier.

Being familiar with the drugs, knowing what the side effects are, knowing what the efficacies are, and then finding these patients are going to be really important. I look forward to having a discussion about the data with all of you.

Dr. Mocharnuk: And what about immunotherapy? What can you tell us about PD-L1 testing and currently available immunotherapies?

NCCN Guidelines®: Immunotherapy for Advanced or Metastatic Disease

PD-L1

- Co-regulatory molecule expressed on tumor cells
- Inhibits T-cell–mediated cell death
- T-cells express PD-1, which binds to ligands
- T-cell activity is suppressed in the presence of PD-L1
- Checkpoint inhibitor antibodies block the PD-1 and PD-L1 interaction
- IHC for PD-L1 used to identify disease most likely to respond to anti–PD-1/PD-L1
  - Based on TPS: % of viable tumor cells showing partial or complete membrane staining at any intensity

	PD-L1 ≥1%-49%
Nonsquamous	• (Carboplatin or cisplatin)/pemetrexed/pembrolizumab (preferred) • Carboplatin/paclitaxel/bevacizumab/atezolizumab • Carboplatin/nab-paclitaxel/atezolizumab • Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) • Nivolumab/ipilimumab • Pembrolizumab
Squamous	• Carboplatin/(paclitaxel or nab-paclitaxel)/pembrolizumab (preferred) • Nivolumab/ipilimumab/paclitaxel/carboplatin • Nivolumab/ipilimumab • Pembrolizumab

	PD-L1 ≥50%
Nonsquamous	• Pembrolizumab (preferred) • (Carboplatin or cisplatin)/pemetrexed/pembrolizumab (preferred) • Atezolizumab (preferred) • Carboplatin/paclitaxel/bevacizumab/atezolizumab • Carboplatin/nab-paclitaxel/atezolizumab • Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) • Nivolumab/ipilimumab
Squamous	• Pembrolizumab (preferred) • Carboplatin/(paclitaxel or nab-paclitaxel)/pembrolizumab (preferred) • Atezolizumab (preferred) • Nivolumab/ipilimumab/paclitaxel/carboplatin • Nivolumab/ipilimumab

IHC, immunohistochemistry; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score.
Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020.

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Dr. Borghaei: Immunotherapy is truly a revolution in the treatment of non–small cell lung cancer. It's been the case for a number of other malignancies such as bladder and melanoma. But in the world of lung cancer, this was revolutionary. For patients who do not have the specific targets that we have been referring to, immunotherapy can offer a long-term benefit.

I have to admit that it does appear that only about 15%, 20% of patients are really benefitting from immunotherapy. But even those who don't have long-term benefit do draw some short-term benefit from the addition of immunotherapy to their standard treatment.

The biomarker that we've selected as a result of all these studies is PD-L1, which is detected with an IHC-based assay. There are many different IHC-based assays for detecting PD-L1, based on the clinical development of all the PD-1 or PD-L1 inhibitors that we have in the clinical practice.

The bottom line is that even though we don't consider PD-L1 to be a perfect biomarker, it is a biomarker that the data support its use as an indicator of how a patient might do in response to immunotherapy. Meaning that the higher the level of PD-L1 expression, the higher the likelihood of a patient responding to anti–PD-1 or anti–PD-L1 therapy.

I use the information in deciding whether I want to use immunotherapy alone or immunotherapy plus chemotherapy in the patient population that I deal with, and I hope I get an opportunity to discuss that with you. But nonetheless, it has become one of the markers that we utilize when we are looking into either clinical trial participation for our patients or standard-of-care treatment. It is an important biomarker to keep in mind. A lot of labs have developed different techniques and pathways to perform the testing and offer it to clinicians.

Dr. Mocharnuk: Thank you, Dr. Borghaei. As you've just indicated, there are many gene alterations in non–small cell lung cancer that inform the selection of therapy. This makes the testing of lung cancer specimens vitally important. For the last part of our discussion today, would you talk a little bit about treatment planning for patients with actionable mutations? Would you also explain how you inform patients and their caregivers about what biomarker results mean, and the importance of a multidisciplinary team in patient management?

Interpreting and Communicating Biomarker Testing Results

Dr. Borghaei: Lung cancer has become really a multidisciplinary disease site in terms of care of the patients. Even in the metastatic setting, we use a lot of the resources that probably up to now, we have not been using. So we need close collaborations with pathologists, and radiologists, and a pulmonary group, especially if they're involved in helping us manage specific toxicities such as pneumonitis or to obtain additional tissue. So the multidisciplinary aspect of care for patients with non–small cell lung cancer has become even more important.

There is a lot of information to discuss with the patient at the time of initial diagnosis. We just covered a whole set of molecular tests that we have to obtain. It is important to communicate the importance of these with a patient, and with patient caregivers. We know that it is overwhelming to get a diagnosis of lung cancer, especially metastatic lung cancer. So being able to discuss the nuances of care as they happen with 1 or 2 family members becomes really important. It's always better to have more than 1 pair of eyes and ears to hear and see what it is that we're seeing in the office because it is a lot of information for patients to digest. Therefore, that help, is welcome.

Helping patients in a shared decision-making process to arrive at a treatment that patients are comfortable with is also important. I don't think we can forget that quality of life is really important to a lot of our patients. Some of the side effects that we talk about in terms of clinical trials, and I'm guilty of that, looking at grade 1 and 2 toxicities and saying, oh, this drug is well tolerated. Well, you know, it's one thing to be the patient who has grade 2 toxicities, and quite another to be the physician who just prescribed the medicine.

Discussing some of these side effects, which sometimes can be chronic over the life of using the drug, is important. Having that shared decision-making process and getting the patient family members involved is really important in helping us understand what the patients have in mind, and what their goals are. Then we try to guide the patients and provide all the information that we can, and help them make the right treatment decision by offering treatment options.

This goes back to the fact that if you don't have all the information, it becomes difficult to offer the best treatment option for the particular patient. As far as I'm concerned, having all the information requires molecular testing, which we've discussed.

I understand how hard it is to get molecular testing. However, it is important, and we need to do what we can to get what we need to come up with the best treatment recommendation for our patients.

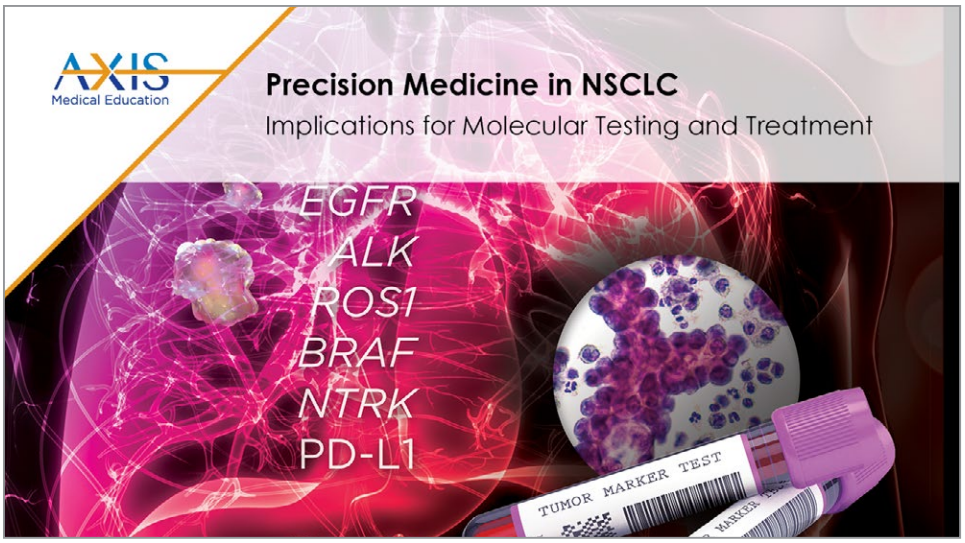
- **Dr. Mocharnuk:** Would you provide us with some key take-aways from today's presentation and biomarker testing in non–small cell lung cancer?

  Dr. Borghaei: Take-away number 1, every patient with history of advanced non–small cell lung cancer, regardless of histology, deserves to have a next-generation sequencing comprehensive panel performed on their tumors to identify potential targetable lesions for which we have really good drugs already available. Or we have really good clinical trials where the possibility of exploring a new drug is there.

  Key point number 2—this is multidisciplinary care. You have to be in touch with your pathologist. You have to know your molecular lab. You have to know what it is that you're asking for and what you want with the precious tissue that you have.

  And take-away number 3 would be to get a really close look at the liquid biopsy panels. In many cases, getting 2 tubes of blood and sending it for an analysis is much easier than wanting to repeat the biopsy or getting more tissue. But keep in mind that if the blood-based assay results do not give you an answer and are negative, you still have to perform tissue testing to ensure you haven't missed anything.

  Those are the major take-aways that I hope you take with you from this discussion. Thank you.



- **Dr. Mocharnuk:** Thank you, Dr. Borghaei, for this excellent review. And thank you to our audience for your participation in this activity.

REFERENCES

Ettinger DS, Wood De, Aisner DL, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020. © 2020 National Comprehensive Cancer Network, Inc. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. *J Mol Diagn*. 2018;20(2):129-159.

Tsao AS, Scagkuittu GV, Bunn PA, et al. Scientific advances in lung cancer 2015. *J Thorac Oncol*. 2016;11:613-638.

US Food & Drug Administration. May 6, 2020. FDA approves first targeted therapy to treat aggressive form of lung cancer. https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-treat-aggressive-form-lung-cancer

US Food & Drug Administration. May 8, 2020. FDA approves first therapy for patients with lung and thyroid cancers with a certain genetic mutation or fusion. https://www.fda.gov/news-events/press-announcements/fda-approves-first-therapy-patients-lung-and-thyroid-cancers-certain-genetic-mutation-or-fusion

US Food & Drug Administration. 2020. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

Velcheti V, Pennell NA. Non-invasive diagnostic platforms in management of non-small cell lung cancer: opportunities and challenges. *Ann Transl Med*. 2017;5(18):378.

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