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Oncologistics

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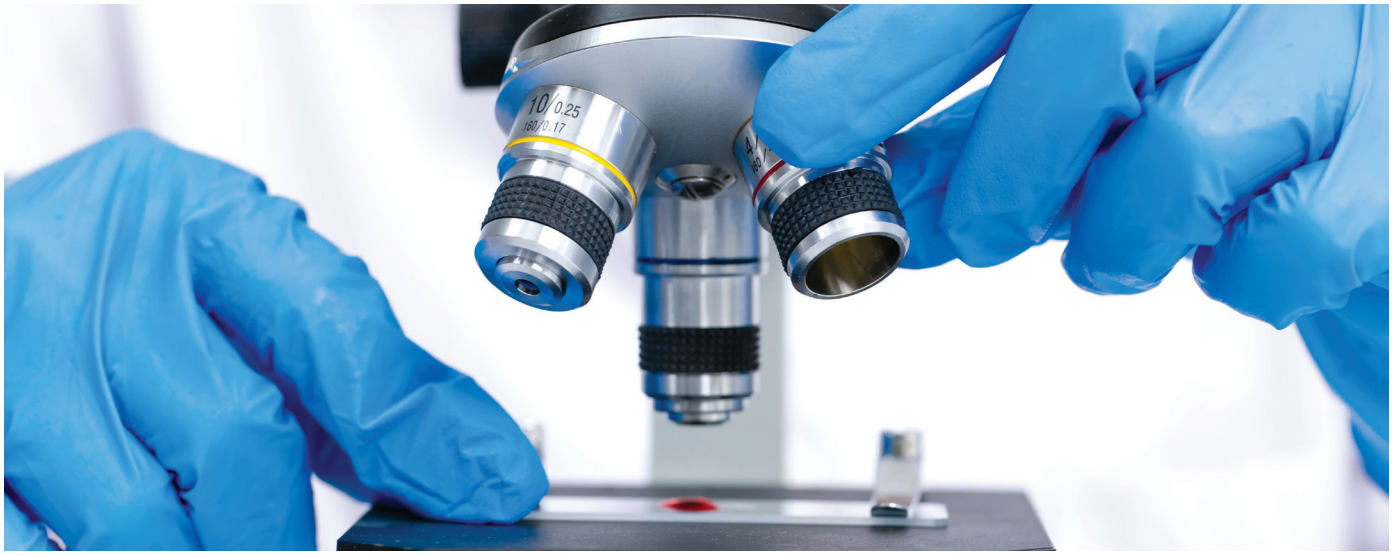

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Paradigms and pharmacogenomics

A conversation with Dr. Howard McLeod, FASCO, FCCP, and Dr. Jai Patel, PharmD, BCOP, CPP

The evolution of cancer care is advancing quickly. Genetic sequencing has radically improved our ability to get the right drug to the right patient—improving outcomes for both patients and practices. But policy is unclear, and lab testing can be interpreted differently. In this conversation, we take a look at the paradigm shift in cancer care, the role of genomic testing and sequencing, and how to navigate this evolving landscape to your practice's advantage.

Howard McLeod: It's timely to be talking about the way that genomics has started to integrate into oncology. You know, it wasn't that long ago when Dr. Patel and I were discussing how someday this might happen. And now it's becoming a big deal in terms of tumor sequencing. It's becoming a bigger deal in terms of the germline. Of course, heritable cancer has been around for a while. But from a policy standpoint, from a technology standpoint, and from a practice standpoint, it's becoming an important part of care.

Jai Patel: It's interesting if you think about how long it's been since that first human genome was sequenced, and we're sitting here almost 20 years later, still trying to identify the most appropriate and standardized mechanisms to integrate genomics into the clinical setting.

And obviously I think we knew it wasn't going to be done overnight, or even over a matter of a couple of years, but I still remember when I was doing my fellowship with Dr. McLeod. At that time, we were just learning about some of the early kind of low-hanging fruits of genes that we should be considering integrating into practice and moving over to a setting where I'm sort of in a community/academic hybrid cancer hospital.

That's a multi-site large hospital; we've got 25 to 30 sites and are trying to figure out how we can now scale this up across the system. And I think we're at an inflection point now with making big decisions about how we bring this to the point of care in real time, and make it as easy as possible for clinicians, because we're all working with very busy clinicians, and it's a large amount of data. So, we're trying to figure out how we can summarize this data into what providers need to know while they're sitting next to the patient's bed—or their chair in the outpatient setting—and applying that information to practice. One thing we're looking at now is testing availability, which I think is no longer much of an issue, at least for where most of us are located.

So, I think there's plenty of tests available. And I think we're now trying to figure out how to digest those results in an integrated workflow that's not going to be too disruptive for our providers.

Howard McLeod: It wasn't that long ago when a medical oncologist had to be a medical toxicologist—as in, they had to be able to wisely choose the best therapies and then manage the side effects to get the patient through the whole process. Now they've had to become a vascular biologist. Now a growth factor cell signaling expert, now an immunologist… and who knows what's coming next. And really what we're finding now is that people can be most successful by learning how to use technologies to help them. So they can direct their intelligence where it's needed, be bright at what they need to be bright at, but then they don't have to carry all that water. That information is sitting there until it has to be used.

That can happen in the form of an electronic system like VieCure. It can be on an app. It can be in the mind of a specialist. I mean, the idea that you have to know infectious disease as well as oncology at most centers—you have either a physician or a pharmacist who can come in and share their expertise.

And I think, in this information overload time—it's only information overload if you let it. Otherwise, it's really a fantastic opportunity to go forward, but we must have the right tools and that's the challenge. That's going to be some folks who are doing cutting edge research and some other folks that are seeing all sorts of different patients and doing the best they can, and they all need help. And we can democratize this by getting the kinds of tools to make it useful.

Jai Patel: Even simply from a clinical perspective, if we take the genomics piece out of it, there is so much clinical information out there. The amount of new drug approvals in the oncology setting, along with the new immune checkpoint inhibitors and other immune-based therapies makes it very difficult to keep up with this information. That's especially true for community practicing oncologists who are seeing everything from myeloma to breast cancer to sarcoma, and to know and understand the most appropriate treatment options, which now include genomic based therapies, targeted

therapies, immune based therapies, etc. It's difficult to keep up with that information and to be able to have best practices at your fingertips, which is why we use internal clinical pathways that can be accessible on an iPad or an iPhone directly for the clinician, as well as leveraging technology to help us with clinical trial options. Because, like you said, there's really no one person that can really know everything and do everything and see 30 patients, 40 patients a day—it's impossible. And so, I think that's why it is critical that we're able to leverage technology. From everything from purely clinical treatments to how we integrate patient characteristics, genomics, and drug interactions. And then how do we ultimately provide the best care to each individual patient using all those factors?

Howard McLeod: The examples you use, coming back to the genetics piece of it, really highlight some of the challenges for most. The right semantic or genome sequencing platform for a myeloma versus a breast cancer versus a sarcoma can be quite different. I mean, you need to make sure that the platform detects fusion, gene fusions for sarcoma. You need to make sure the right genes are on the platform for myeloma. Often the genes are not important for breast or for sarcoma for breast. You know, you want to be looking at a homegrown resistance with something like ESR1, in addition to the tyrosine kinase work there or other variants.

You now have a few tissue agnostic approvals. Breast cancer, a sarcoma could receive the same thing, or something like that. And I think often the technologies are sold to the individual oncologist as a one-size-fits-all: the irony, given that we're trying to do personalized medicine.
You at the least have a heme and a solid tumor choice. Don't expect that one platform will do the whole thing. I guess if we do whole genome sequencing of a tumor, then that's fine. But often that takes too many resources to accomplish. We're seeing that on the germline side, in the supportive care elements—you've highlighted a lot of those areas as well.

Jai Patel: Yeah, which we know can be applicable across the board in many different settings regarding the supportive oncology and pharmacogenomics and trying to better understand how patients are going to respond to, let's say, opioids or antidepressants, and integrating that into the workflow among other things like drug interactions and phenol conversion. And that's why I think the way we retrieve this information, and the way it's consumed by providers, is really important.

Every clinician may have a different point of view of what they want to see, how they want to see it, what information they want and don't want. So how do we provide considerations of using the information in practice, and how do we try to make it as streamlined as possible to ensure that they're getting the most important information in a concise manner that is actionable. I mean, it's got to be actionable. It must anticipate the needs of the physician and it must be adaptable to scientific literature that is constantly evolving. And so, these mechanisms of how we're delivering that information must be adaptable to new genotype, phenotype translations. It must be adaptable to new evidence coming out because that's going to be kind of the filter of how we're going to receive this data.

Howard McLeod: This is a little bit of a controversial point. You and I both see the molecular pathologists do an excellent job turning the results from a sequencer into some clear gene variant information. So, when a molecular pathologist puts out a report, I have full confidence that that really is that gene that has that alteration. That it is present.

So that's been a relatively recent advance, you know, having someone properly trained like the pathologist do that reporting. That's a key piece, whether it's for germline use for supportive care oncology, whether it's the somatic stuff or for choosing a therapy: chemotherapies or targeted therapy.

But there's this gap between the end of the report and the medical decision. And we're seeing now more need for medical review. And when I use that term, because they remind me that they have an empty tube but more of a therapeutic review, let's say, "Well, yeah, you have these three alterations, but I would use drug B first followed by drug C followed by drug A or clinical trial," you know, something that you didn't even consider.

And you know, we see the same thing on the germline side: saying that someone's a poor metabolizer is not the same as helping oncologists know what to do for pain control for antidepressants, for all these other different areas.

Jai Patel: Yeah. You know, it's kind of funny because when we do, whether it's a panel of pharmacogenomics or we're doing molecular sequencing of the cancer, it's one of those things where you're doing it because obviously you want to better inform medical management. And you're hoping to probably find something that you wouldn't have thought was there in the first place. Right? I mean, we do reflexive testing for lung cancer, for example. But really what we're looking for is if there is something present that we're not currently testing for, and if we don't see anything, we're almost like, "Aw, darn." Like there's nothing else. "Darn I don't have

anything else to help me choose another therapy."

But then when it comes back and suddenly, you've got a tumor mutation burden of 38 mutations per megabase, and you've got 50 different mutations, translocations, and fusions that have popped up. And like you said, it's where do you start first? What do you do first? And technology is a good place to start to filter that data. But like you said, there also must be some degree of human involvement as we're the ones treating the patients to say, "Okay, based off of the clinical data, based off of the patient's characteristics, their picture, this is how we should approach this."

These are the ones that are approved, not approved. This is where we have clinical trial options, etc. And so, we've got a kind of cascading effect where we're starting off with 50 different things. How do we narrow it down to that one?

Howard McLeod: Well, and you find that on both sides. Many oncologists have either bought in that the germline is important or bought in that the somatic genome is important, but don't realize you could have both. We always talk about risk benefit—well, that's germline and somatic. You know, you're going to see a lot of risks as well as some of efficacy dosing and so forth on the germline. Then of course you're able to choose from different targeted therapies: immunotherapy from the somatic stuff, getting away from "which genome are you looking for?" and getting toward "how do we help this patient?"

I think is, at least the lens that I've tried to use with some folks it's like, this is not a debate on whether germline is viable. Rather, this is application. Most oncologists do not do all that training. Being good at prescribing antidepressants or providing the supportive care is what they do because they must, not because that's what they train for. And so, I think especially the supportive care pharmacogenomics, being able to help them get it right more often is incredible.

Jai Patel: Yeah, absolutely. And even things just like simply identifying the most appropriate dose for certain cancer therapies and chemotherapies. I mean, that information is critical, and a lot of our providers are now realizing, since we started doing this, how informative things like DPYD testing can be, for example, for a drug that's been around since the 1950s. And I think now it is becoming a lot more widespread regarding testing. We only now really have maybe four or five variants we feel are clinically actionable, but over a hundred have been identified.

I mean, you've been there from the beginning of identifying and discovering some of those snips and I think we're going to continue to identify more as folks transition from more targeted panels to more whole exome, whole genome sequencing-based panels, which will continue to drive research while informing medical management.

Howard McLeod: You know, you make a good point as well about the value of testing. If we were to discover the BRCA1 gene today, or the BRCA2 gene today, we would not call it the BRCA. We would

"If we were to discover the BRCA1 gene today, or the BRCA2 gene today, we would not call it the BRCA. We would call it just 'CA' because we're finding it to be important for prostate, for pancreas a bit, and for a bunch of other tumors."

call it just "CA" because we're finding it to be important for prostate, for pancreas a bit, and for a bunch of other tumors. And breast and ovarian, as you know, has the highest frequency of germline—your CA1 and 2 variants are not breast and ovarian, it's prostate, it's some of these others. It took years to figure that out, but it was because nobody bothered to look. And as we're doing more with germline sequencing, finding new variants for all sorts of different applications on the somatic side, finding new variants, finding new genes, finding new applications of genes… really, we're making the case.

Especially with the therapeutic drivers now for the inherited cancer genes where we're now looking and finding, for example, an 80-year-old with non-small cell lung cancer with a BRCA1 variant that is germline and should have caused her new breast cancer many years ago. Well, it didn't. So, it's really opening how much we've been looking at what we noted look at, as opposed to really stepping back and learning more.

Jai Patel: Absolutely. And you know, you bring up a great point about the value of all this. I think a lot of us clearly see the clinical value, but there are folks who want to see the monetary value as well. Given the large application of pharmacogenomics, so many landscape analyses have shown that well over 98 percent and 99 percent of individuals carry at least one genetic variant that could be informative during their lifetime for some medication. So, it's highly applicable as we do more large-scale testing of not just one or two genes, but you know, most panels out there might be 20, 25 genes. And like we talked about, transitioning to things like whole exome and whole genome sequencing. It's a lot bigger bang for our buck, right? I mean, it used to cost thousands of dollars, hundreds of millions of dollars to get a whole genome sequence. Now, obviously we're down to maybe less than a thousand dollars and that information is valuable for a patient for their lifetime.

We must realize many of these patients are being treated in community settings or even academic settings or may be treated within that health system for their lifetime. (They may go other places, but it's very likely a lot of these patients get treated in one particular health system.) So, to be able to provide that information across disciplines, across oncology, to their primary care doctor, their cardiologists, so on and so forth will ensure that this one gene could be applicable for five different drugs that they may receive in their lifetime. And we would run into situations when we didn't have the clinical decision support that patients would be enrolling into trials. They'd be getting genomic information. It would end up being used once and then done. And so, I think that's where again, bringing in that technology and that decision support to say 10 years later, this can still be informative.

Howard McLeod: That is so key. I think we've all seen situations where a heritable cancer risk was not passed on to the next clinician. And, you know, something was missed. They didn't get scoped, they didn't get mammography, and then something bad happened. The same thing is at risk for the way we use cancer genomics, knowing someone is a poor metabolizer and then giving them a pain med that requires that metabolism. That's basically giving a placebo, it's not going to give them an effect if that information is not passed on.
So, how do we make it so that we optimize a patient's cancer care? But also, so they'd benefit from matching? A patient may need other specialties and there's some real challenges there to get that all in.

Jai Patel: Absolutely. And as you know, there are lots of resources regarding the most appropriate genes we should be looking at and the most appropriate appeals. How do we integrate that information? How do we translate from a raw genetic result into a clinically actionable prescribing decision?

It's important for folks to realize and understand that these resources are available. Again, testing is available, and resources on how to apply that information are available. Technology is available and now it's almost playing like a beautiful mind and trying to figure out how do we use everything altogether. As again, we're at the bedside. And as you know, I have looked at the regulatory part of this too, right? I mean, direct to consumer testing is becoming a big thing.

Patients are showing up to our door with genomic information and they're asking for it and they're asking their providers, "Please use this." Or "how do we use this to manage my care?" So, we've got to be ready to prepare our frontline providers to discuss how they're going to apply that information with their patients.

Howard McLeod: That's so important. And I think we'd like to say we're patient-centric; I've been in places where we've had a patient first initiative. And what that meant is to try to make it more convenient for us to see patients—not trying to make it more convenient for the patient. The idea that you have come in two hours at a time for your colonoscopy, not because you need to, but because that way you're there sitting around when we're ready. And you on the genomic side as well, making sure that we test early for the panel, like you mentioned, so that we're ready for what happens.

You know, I still see even today people testing for one or two genes at a time on the tumor side of things, genes at a time of the germline. First, it's a waste of money because you can get a bunch of genes for the same cost or less. It's a waste of precious tissue on the tumor side, because it's so hard to get enough tissue with that biopsy, that fine needle aspirate. It's a little bit easier with the buckle scrapings of the saliva or the blood for germline. But then you can also be prepared for things in the future, and this idea of being preempted and being ready to avoid trouble is something that we haven't had the luxury of in oncology. But now we can avoid a drug that's not going to work, or we can avoid a drug that's going to cause harm—both with germline and somatic testing.

Jai Patel: You're absolutely right. I think there's a lot of potential here, a lot of application, and we're in a very busy environment trying to figure out how to filter this down for a given clinician and to allow for patients to receive that. You know, the kind of precision, personalized medicine we all talk about and we all dream of.

Howard McLeod: I will leave us with this. We had a few patients where we looked deeply at their somatic sequence and germline, and we didn't find anything to help us choose a therapy. And then later we got a thank you note back from the family, and we contacted them to say, "Why did you thank us? We found nothing." And their response was that they now know that every stone was turned over for their family member, and we did everything we could; we can now move forward, knowing that we did everything. You can't monetize that; you can't go forward. But the idea that even when we don't find anything, it still is valuable information, steering things forward for the family. Giving them that confidence that they're doing all they can. We can't cure everybody yet, but at least we know—and we're doing all we can at the time.

Dr. Howard McLeod, FASCO, FCCP is an internationally recognized expert in precision medicine who made novel contributions at the discovery, translation, implementation, and policy levels.

He is the Medical Director for Precision Medicine at the Geriatric Oncology Consortium and a Professor of Medicine and Pharmacy at the University of South Florida. Dr. McLeod chaired the NHGRI eMERGE network external scientific panel for the past decade and was a recent member of both the FDA committee on Clinical Pharmacology and the NIH Human Genome Advisory Council.

Dr. Jai Patel, PharmD, BCOP, CPP is Chair, Department of Cancer Pharmacology and Pharmacogenomics at Atrium Health's Levine Cancer Institute and Associate Professor in the Division of Hematology/Oncology. Dr. Patel leads translational and clinical pharmacogenomics research, including implementation science, at Levine Cancer Institute. His projects range from gene discovery and translational studies to prospective interventional trials using pharmacogenomics to optimize anticancer and supportive care medications. Dr. Patel serves as co-investigator on phase I trials and directs blood collection for clinical trials across the cancer center. He also serves as a medical liaison for the Department of Clinical Trials and as a Clinical Pharmacist Practitioner in the Department of Supportive Oncology. He is a member of the VieCure Clinical Advisory Board.

NON-SMALL CELL LUNG CANCER (NSCLC)
BIOMARKER TESTING LANDSCAPE

Progress in NSCLC

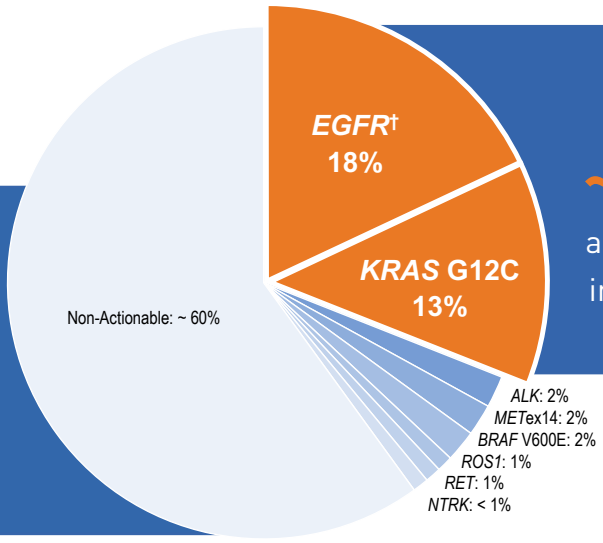
The biomarker landscape has evolved in recent years

- **More than 20 targeted therapies** have been approved **for use in NSCLC**[1]
- **~ 60% of cancer therapies** launched in the US between 2015 and 2020 **require or recommend biomarker testing prior to use**[5]

Prevalence of Actionable Oncogenic Drivers in NSCLC

~ 2 in every 5

patients with non-squamous NSCLC have an actionable driver mutation[6,*]



KRAS G12C and *EGFR* make up **~ 75%** of all actionable drivers in non-squamous NSCLC[6]

*From a 2020 analysis of patients with NSCLC in the AACR Genie database (v8.0, N=14,485) and prevalence of *KRAS* G12C and mutations or alterations with an annotation of "FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication" in non-squamous patients.[6]

†*EGFR* prevalence does not include exon 20 insertions, which can be found in ~ 2% of the overall NSCLC population.[7]

Guidelines Recommend Broad Molecular Testing for Eligible Patients With Advanced NSCLC[8,9]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Recommendations[8,‡,§]

	Molecular Biomaker								Immune Biomaker		Molecular Biomaker	
Actionable	*EGFR*	*KRAS* G12C	*ALK*	*MET*ex14	*BRAF*	*ROS1*	*RET*	*NTRK1/2/3*	PD-L1	Emerging	*MET*amp	*HER2*

Testing should be conducted as part of broad molecular profiling

Single-biomarker immunohistochemistry testing recommended

Expanded-panel testing recommended

‡The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories.[8]

§The NCCN Guidelines® for NSCLC recommend broad molecular testing to identify rare driver variants for which targeted therapies may be available to ensure patients receive the most appropriate treatment.[8]

- **CAP/AMP/IASLC guidelines recommend testing for actionable and emerging biomarkers utilizing a comprehensive panel or targeted testing**[9]

AACR, American Association for Cancer Research; ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; BRAF, proto-oncogene B-Raf; CAP, College of American Pathologists; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IASLC, International Association for the Study of Lung Cancer; KRAS, Kirsten rat sarcoma; MET, mesenchymal-to-epithelial transition; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed cell death ligand 1; RET, rearranged during transfection; ROS1, c-ros oncogene 1; TMB, tumor mutational burden.

Guideline-Recommended Biomarker Testing May Improve Patient Outcomes[10,*,†]

Adherence to testing for guideline-recommended biomarkers, regardless of therapy

Decreased mortality risk by **11%**

*This was a retrospective study of 28,784 patients diagnosed with advanced NSCLC. Adherence to biomarker testing consisted of patients with evidence of testing for any biomarker, including *EGFR*, *ALK*, *BRAF*, *KRAS*, *ROS1*, or PD-L1 between 14 days prior to and 90 days after diagnosis of advanced NSCLC and the main outcome, overall survival (OS), was agnostic to treatment.[10]

†Multivariable analysis was adjusted for age at diagnosis of advanced NSCLC, sex, smoking status, and stage at initial diagnosis of NSCLC.[10]

Many Patients With Newly Diagnosed NSCLC Do Not Receive Broad Molecular Testing[11]

~ 50% of metastatic patients received comprehensive biomarker testing[11,‡]

Regardless of patient characteristics such as age, race, and smoking status, **biomarker testing** should be conducted in **all eligible patients** with advanced NSCLC[12]

‡A retrospective, observational study assessing real-world biomarker testing patterns in 3,474 patients with metastatic NSCLC from community oncology practices within The US Oncology Network between 2018 and 2020.[11]

Additional Considerations for Comprehensive Biomarker Testing

Addressing Tissue Insufficiency

- Multigene testing can reduce the number of ordered assays and conserve tissue needed to assess all actionable biomarkers[12]
- Rapid On-Site Evaluation (ROSE) assesses sample adequacy for molecular diagnostic studies to potentially help reduce rebiopsy rates[13]
- Liquid biopsy, which has a high degree of concordance (> 98.2%[§]) and improved turnaround time, can be used when tissue collection is not feasible[14]

Shortening Turnaround Time (TAT)

- Broad molecular testing at diagnosis may take less time than consecutive single-gene testing, a process of elimination approach[15]
- Reflex testing protocols can reduce average TAT by 37 days[16]

Consistent Reporting

- Consider including all actionable biomarkers at the beginning of the report using established nomenclature for genetic alterations[17]

§Overall concordance across four genes (*EGFR* exon 19 deletion and L858R, *ALK* fusion, *ROS1* fusion, and *BRAF* V600E).[14]

Learn more at FindKRASG12C.com

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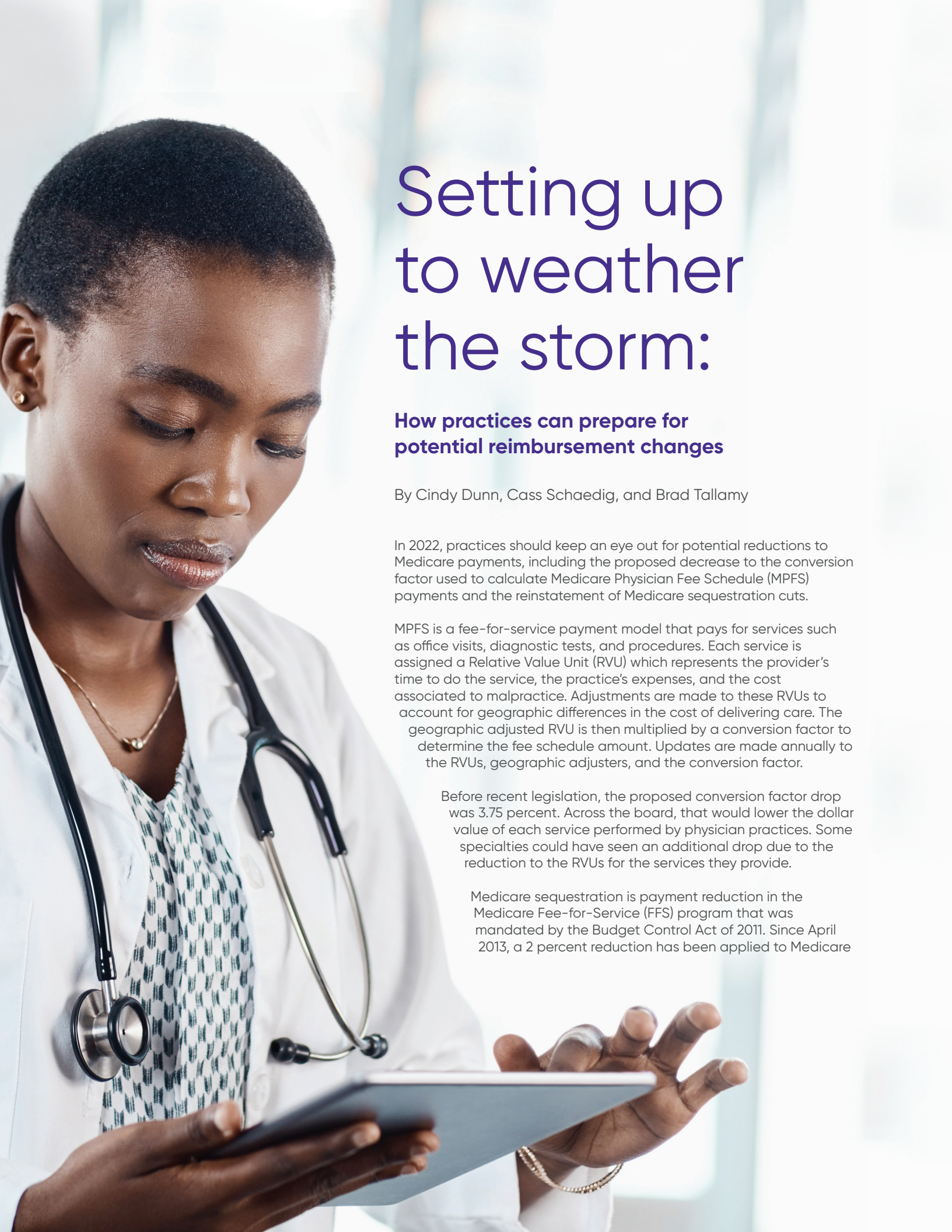

Setting up to weather the storm:

How practices can prepare for potential reimbursement changes

By Cindy Dunn, Cass Schaedig, and Brad Tallamy

In 2022, practices should keep an eye out for potential reductions to Medicare payments, including the proposed decrease to the conversion factor used to calculate Medicare Physician Fee Schedule (MPFS) payments and the reinstatement of Medicare sequestration cuts.

MPFS is a fee-for-service payment model that pays for services such as office visits, diagnostic tests, and procedures. Each service is assigned a Relative Value Unit (RVU) which represents the provider's time to do the service, the practice's expenses, and the cost associated to malpractice. Adjustments are made to these RVUs to account for geographic differences in the cost of delivering care. The geographic adjusted RVU is then multiplied by a conversion factor to determine the fee schedule amount. Updates are made annually to the RVUs, geographic adjusters, and the conversion factor.

Before recent legislation, the proposed conversion factor drop was 3.75 percent. Across the board, that would lower the dollar value of each service performed by physician practices. Some specialties could have seen an additional drop due to the reduction to the RVUs for the services they provide.

Medicare sequestration is payment reduction in the Medicare Fee-for-Service (FFS) program that was mandated by the Budget Control Act of 2011. Since April 2013, a 2 percent reduction has been applied to Medicare

payments for all services, including buy and bill services such as drugs and supplies. To assist practices struggling with the financial strain brought on by the pandemic, the government put a pause on sequestration from May 2020 through March 2022. This will be followed by a reinstated 1 percent reduction in payment through June 30, 2022.

The amount of money a provider is receiving due to sequestration relief is dependent on the volume of traditional Medicare patients and the type of services billed. For example, our analyses show that a typical oncologist is receiving an additional $5,332 more per month for services while the government has paused sequestration.

Reports within our analytics platform can show the impact of both the proposed 2022 Medicare Fee Schedule and the reinstatement of sequestration. While sequestration applies to only traditional Medicare patients, many Medicare Advantage and commercial payers base their fee schedules on the Medicare rate so changes made by Medicare can have a rippling impact on other payers.

Uncertainties ahead

The uncertainties of COVID-19 and emerging variants also come into effect. We don't know what will happen next year. Fluctuations in patient volume coupled with reduced reimbursement due to fee schedule changes and reinstatement of sequestration could have significant impact to the practice's cash flow. It's difficult for all practices to navigate these waters, but particularly small, independent practices.

What to do: Better track money coming in and out

Practices need accountability of funds. When the pandemic hit, there were ways to get additional money through the paycheck protection program and CARES act. Money came in to help practices pay bills and keep their staff, even though there were fewer patients.

Any healthcare provider that received at least $10,000 from the Provider Relief Fund (PRF) during the first half of 2020 had to report on its use of those funds by September 30, 2021. Many terms and conditions accompanied the acceptance of these payments and all recipients needed to submit data sufficient to demonstrate that funds were used for healthcare-related expenses or lost revenue attributable to COVID-19. Whether or not a clinic was able to carefully account for their spending during a pandemic is going to become an important question.

Now, specialty physician practices are without those extra monies coming into the practice and could face reduced payments in the New Year. Formulating a budget that will help meet overhead expenses without this additional financial help will be paramount.

During a recent webinar, we polled practice staff to ask, "How much has your practice planned for reintroduction of sequestration?" Two-thirds of respondents chose "Little to none."

What to do: Participate in grassroots campaigns

Our specialty physician practices took action in April 2021, when providers sent nearly 1,500 letters to their Congressional representatives urging the sequestration moratorium be extended. Due in part to this organized effort, the moratorium was successfully extended. Practices can use Community Counts to identify their representative and start another grassroots campaign in the future.

The conversion factor is law, but for 2021, Congress added an additional $3 billion to the Physician Fee Schedule to offset the decrease. The recent bipartisan infrastructure bill actually extended sequestration to help pay for that agreement. Congress has clearly signaled its intention to reinstate sequestration at some point. Will it be in 2022?

A lot rides on what happens this winter with the Delta and Omicron variants, and others. If schools are open, if patients can get into practices, if hospitals are not overwhelmed, those cuts will likely go back into effect. Policymakers may consider an extension if major physician groups push for one. Members of Congress care more about hearing from physicians in their states than lobbyists in D.C.

It's best for the practices to plan for the sequestration moratorium to go away at some point and be financially prepared for the reduction.

We oppose efforts to cut Medicare Part B reimbursement, which causes significant financial strain to community provider csustomers. Learn more about our advocacy at Community Counts: communitycountsadvocacy.org

Unscripted:

Precision medicine evolution with Susan Weidner and Natasha Clinton

The Precision Medicine Advisory Panel is made up of oncologists, pharmacists, nurses, and administrative staff, all of whom bring their experience, perspectives, and industry knowledge to keep our members informed about advancements in the field.

We recently sat down with Susan Weidner, Senior Vice President of IntrinsiQ Analytics, Natasha Clinton, Director of Medical Affairs for IntrinsiQ Specialty Solutions, and Nicole Chambers, Senior Director of Corporate Services for ION Solutions, to discuss the overall strategy for ION's precision medicine program. From the creation of the Precision Medicine Advisory Panel to the future of precision medicine, our discussion also verged into advancements in liquid and tissue biopsy testing, and improvements our partners are making in the precision medicine space.

Let's begin with the Precision Medicine Advisory Panel. Can you share some background?

Susan Weidner: Sure. We've really tried to establish the Precision Medicine Advisory Panel as a group of experts who, on a day-to-day basis, are engaged in how to advance the adoption of precision medicine from a practice perspective. That requires having someone who understands about the scientific aspect of how those lab tests are developed, how to interpret them, and then how to implement them from a clinical perspective for all the different types of providers—physicians, pharmacists, or nurses in the practice. By establishing this multidisciplinary panel, we hear multiple perspectives to optimize both the clinical workflow and the scientific impact of utilizing precision medicine testing.

Natasha Clinton: We have physicians, pharmacists, and nurses on the panel, so it's really a holistic approach when we think about not only the clinical and scientific processes that surround precision medicine and testing, but also the operational aspects and challenges or barriers to testing. It's important that we have those conversations with the panel so that we fully understand the barriers that may prevent testing, but also then collectively as leaders in the space bring together solutions that would help address those challenges and support our members as they're looking at ways to increase testing within their practice.

Can you share your thoughts about how we interact with members on a regular basis, and how the panel functions at our live or virtual meetings?

Natasha: We try to meet with the panel at least twice a year live, and then have three to four virtual meetings throughout the year where we connect by phone or video conferencing. In the event of COVID we've had to transition to a virtual environment, but because the panel was already used to working in that way, that's gone very well, and we've been able to continue with the work through a virtual environment.

During those meetings, we have a broad agenda that we cover where we're inviting in partners to learn about new innovations in the space. And then we have breakout meetings depending on the objective or initiatives we're working on, where subsets of the panel will form into working groups and meet to work on various activities. For example, we may be evaluating clinical and scientific data of a potential new testing solution, but we're also working to develop new testing recommendations.

Susan: Part of what we're trying to accomplish in our live meetings is a robust dialogue about the continued challenges they may be facing within the practice with the significant number of new available tests, as well as new indications from a therapeutic option perspective. It's often important for us to make sure that as we're reviewing the testing recommendations, we're incorporating any of the new advances to ensure those are addressed from an operational perspective.

Natasha: It's also important to call out that we've identified disease state leaders, and that process is important because those disease state leaders review those testing recommendations and evidence related to maybe new updates or new areas of focus and update those testing

recommendations on a quarterly basis. They provide scientific evidence to back up any changes or updates they're proposing to the broader panel, and the broader panel reviews the suggested edits and either approves or has dialogue around why we should or should not make changes. Those testing recommendations are then published on our precision medicine center and made available to the broader membership.

Give us some details about the differences between the testing recommendations provided by our panel and the clinical guidelines in the industry.

Natasha: There is a distinct difference in traditionally what clinicians think about related to clinical guidelines or clinical practice guidelines, and the testing recommendations that the panel is developing or has developed. Typically, a clinical guideline is aimed at guiding decisions based on criteria around diagnosis and management and treatment of a disease, and our testing recommendations are really focused around developing simply that. Testing recommendations that are based in scientific data around NCCN guidelines or research, or evidence related to clinical journals, et cetera.

We identified several disease states we wanted to begin developing testing recommendations around, such as breast cancer, lung cancer, and so forth. Over time, we've seen this shift where biomarkers may span multiple different cancers. And so today we're really focused on building those testing recommendations that are focused on maybe a molecular test or testing at a molecular level versus at a disease state level.

So, the recommendations are not aimed at guiding therapeutic choices. They're really aimed at the testing that should be done for a particular patient: when to test, how to test, why should you test. And then particular biomarkers that may be included or should be included for a particular patient based on the clinical scenario.

You started touching on the biomarkers that are used in testing. Can you give some more details about which ones are available, and the corresponding treatments?

Natasha: The number of therapies being at least 50 percent or more by 2025, that will either be a targeted therapy or an immunotherapy—and that really highlights the importance of biomarker testing. Many of those therapies require biomarkers to drive therapeutic decision-making. And so it's vitally important that we understand the testing, and that we're driving the right patient at the right time to the right test so that we can make appropriate clinical decisions that lead to that appropriate targeted therapy or immunotherapy based on the clinical scenario.

It's so key to test these patients because if you don't test, then you don't know that the patient has a biomarker. Current data, if we even looked in the non-small cell lung cancer space, really shows us that patients are not being tested appropriately. And if you don't know what those results are, we haven't been able to test them, then that impacts outcomes because of the appropriate therapeutic decision process.

That makes sense. So, it completely fails on a precision treatment—if you don't even know what you should be doing or looking for.

Natasha: I think that one thing that's important to highlight as well, and one thing we pay close attention to when discussing as a panel and developing the testing recommendations or re-evaluating them at those quarterly intervals, is what's included in a panel. Because many testing companies will have, let's say, a non-small cell lung cancer panel. So, it's important that the clinicians understand the key biomarkers that should be included in that panel to make sure we're not missing something that would give them that fuller picture of the patient. And again, when they come to that decision of "what treatment should I select?" or "what direction do we need to take to help manage this patient?" that all that information collectively is really important when making those decisions.

Tell us a little bit about how you see the broader precision medicine program and where you see it now versus where you see it advancing

Susan: Sure. We've developed the precision medicine program to be a living program that can evolve with where our therapeutic and diagnostic testing are going, and to be flexible as we anticipate more than 50 percent of all medications used within the oncology space will be targeted by 2025. It's important that we continue to emphasize the use of precision medicine testing, especially next generation sequencing to determine the most appropriate therapeutic options.

The new available cell and gene therapies also require us to continue to drive the appropriate use of testing, given that they will target a very specific patient population, and given the high cost of those therapies and the need for potential clinical support outside of the practice. It's very important that our

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"It's very important that our practices think about how testing can be implemented to identify the most appropriate patients for targeted therapies along with immuno-oncology therapies."

practices think about how testing can be implemented to identify the most appropriate patients for targeted therapies along with immuno-oncology therapies. As we continue to evolve, we'll bring additional capabilities to go with the testing recommendations, including the direct incorporation of their lab testing data into platforms that are wrapped around their clinical solutions, such as their electronic medical records. Then we can help to further assess whether we're having the appropriate improvements in clinical care, through quality measurement and education.

Natasha: I think there's just a key point to call out, and Susan touched on this, which is that the panel is very much a working panel. They produce a lot of clinically and scientific-based information, such as the testing recommendations, and really helped to guide some of those decisions as we navigate this fast-paced, ever-changing space that we call precision medicine.

Natasha, can you take a moment to explain what's a liquid test and what's a tissue test, and the difference between the two?

Natasha: Tissue tests have traditionally been (and still are) the standard of care for diagnosing cancer, but with the evolution of liquid biopsies, the science behind the liquid biopsy is really looking at analyzing DNA. In most cases, that's more specifically circulating tumor DNA, which comes off the tumors themselves and circulates in the blood. And so that test is a blood draw where you're taking whole blood from a sample from the patient.

We've seen an evolution of liquid biopsies in the last 18 months—most notably in 2020, with new indications and approvals from the FDA—in whole or next generation sequencing capabilities within liquid. Prior to that, there was more focus on single genes or, depending on the disease state, particular genes that they would evaluate in liquid. And so, with that new indication of the next gen sequencing capability within liquid, that opens a lot of possibilities that didn't exist prior to that.

Can you talk a little bit about how those different tests have evolved and changed?

Natasha: This space has evolved to where we're relying heavily on both tissue and liquid testing, depending on the clinical circumstance. Early in the precision medicine discussions, as we began working more and more with leaders in the space, there were lots of discussions related to tissue versus liquid biopsy. When do you use those? What's the concordance between the testing? When is it clinically relevant to use tissue testing or liquid testing? And I think there was some hesitancy early on with liquid testing just based on consistency of the results between liquid and tissue, and that it's a newer technology. However, over time that has significantly changed and evolved.

We've learned a lot about biomarkers in the last few years, and we continue to see a lot of biomarkers that are emerging in the space. So given the advantages—depending on the clinical situation—that liquid biopsies provide, that gives clinicians a way to monitor specific patients for those emerging biomarkers, whether that be for clinical trials or other new emerging therapies coming out.

Nicole Chambers: The only thing I'll add there is that some of our companies who do have a liquid test have implemented mobile

"This space has evolved to where we're relying heavily on both tissue and liquid testing, depending on the clinical circumstance."

phlebotomy. So, they will actually send the van or truck, whatever they're using, with the qualified healthcare professional to the patient's house to take the blood draw.

Would you say they provide consistent results? Is one more trustworthy than the other?
Natasha: Yeah, I think that was definitely a concern with the providers, related more specifically to the liquid test, but over time we've actually looked at a few case examples, some of our leaders have shared examples where they have received similar or the same results based on tissue and liquid testing on the same patient.

When considering the value of liquid versus tissue testing, I think it's an important call out related to the limitations of the liquid biopsy and how that test is performed. That's dependent on how the tumor is shedding that DNA. It is definitely a consideration when clinicians are trying to make decisions on the best test for the patient and clinical scenario that's sitting in front of them.

Can you also talk a little about the test panels that are required?
Natasha: The test panels can be very challenging to providers, and the challenge really lies in the fact that the panels can vary depending on the testing company, and the grouping of individual tests within a panel. And by that, I mean that certain tests, like specific molecular tests, may be omitted in a broader based panel. And so, it's really important for the providers to understand what's included in the panel, what exactly is being tested, and understand the recommendations or the guidelines around testing for the clinical case that they're sending.

That's a great example of why our panel came together to develop the testing recommendations, and to continue to develop testing recommendations, because we need to make sure that we're not only looking at the broad-based panels, but also at what those individual tests are that are included underneath or within those panels.

Let's discuss payer coverage when taking these tests. How does that work?
Natasha: The payer coverage can be somewhat tricky. Depending again on those panel sets or if you're trying to order a broad base, like a comprehensive genomic profiling test versus a disease specific panel, for example. And so, you know, there are resources out there depending on the testing company that will help address some of the payer challenges that practices, and physicians and patients run into. But that is something that can be of concern, so it's important to have a good relationship with that testing company so they can help assist us with payer coverage issues that may arise. Again, it's also important to have a good understanding as to what's included in that broader set of testing.

Nicole: A lot of these testing companies also have patient assistance programs or foundations that the patient can apply to in order to get discounts or money put toward their testing costs.

Now we're going to move on to Nicole to talk a bit about practice-based testing and some of the partners we're working with on that
Nicole: One partner we started working with is Precipio, a newer company that serves as a reference laboratory. They're focused on hematologic malignancies, and one of the biggest issues in this area is delayed turnaround time on these molecular tests. The FDA mandates that you get results back within five days, and that often does not happen. So, to address that, Precipio created the HemeScreen® panel. Physicians' office laboratories and our practices can purchase a machine called the QuantStudio machine from Thermo Fisher Scientific, and they can run their own tests in their office and have results within four hours instead of waiting two to four weeks. For genes to be tested and reported right now, the genes and the common genes that they can test for are MPN malignancies, as well as AML. They have much more in the pipeline that will be forthcoming. And physicians can either batch these tests together and run them, or they can run them as a one-off as needed. Really the biggest benefit, as I said, is a faster turnaround time, but it's also gaining control of the whole process. Now it's all in the physician's office and they have full control over the testing, and they're able to keep that revenue in-house: they're not sending tests out to a reference lab. They're able to bill for that so it's a new revenue stream for them as well.

One of the other companies we are working with is Invitae. This is a genetic testing company and what they've created, which I found beneficial during COVID, is the Gia® chat bot. "GIA" stands for genetic information assistant, and what it does is it facilitates comprehensive genetic testing with the information intake necessary to understand if a patient is eligible or should receive a genetic test. The Gia chat bot is highly intuitive and intelligent, and it prompts the patient with different questions. At the end of

the chat, it will say whether they qualify for genetic testing.

What the patient can then do is opt to have a test sent right to their house, and they do the saliva test and send it back to their physician for the results. They can then go over what their prevalence or their tendency is toward different mutations. Depending on the patient's results, Invitae will then test the rest of the patient's family at no cost; whichever members of the family would be applicable depending on the type of cancer.

They're a good partner of ours and they've really adapted to being in this COVID environment and having the tests being sent direct to the patient's house. They've also recently purchased Archer DX. ION had been talking to Archer DX for quite a while about in-house NGS testing.

So that tissue testing that Natasha was talking about—Archer has reagents that allow physicians to run the NGS testing that patients need at highly sensitive rates. Often they're able to find at 6 percent greater sensitivity, RET fusions, and some of those more rare fusions or markers that may not be detected on other next gen sequencing tests. So, we're really happy that Archer has moved into the Invitae family, and we'll be bringing them out to practices soon.

You've highlighted some of our current service partners in the precision medicine space. Can you tell us what it takes to become an ION partner?

Nicole: Sure. Natasha and I set up a subgroup of our Precision Medicine Advisory Panel, and we rely on them to kind of vet our partners and make sure that the tests really do what they say they'll do—if they're as specific as they say, or if their turnaround time is the same. Sometimes we'll have members of this little subgroup do a validation study for us to make sure that the partner really stands up to what they say they can do, or we have the partner present to the Precision Medicine Advisory Panel, let them ask questions and really dive deep into the clinical basis of the tests.

So as far as a good partner, we do look for those that are going to be engaged with the Precision Medicine Advisory Panel. Every test is different, it's a different set of genes, or it just has different capabilities. And we need for them to have that ongoing education. We prefer partners that look to engage with us and do some broader education with the panel and the membership going forward. We usually like to sit down and develop a plan to launch them into the membership, but then to also talk about that education component.

Natasha, do you have anything you want to add about your work with the panel and their role in finding new partners?

Natasha: Yes. As Nicole mentioned, we put together a subgroup of the Precision Medicine Advisory Panel to begin to work closely with potential partners to evaluate not only the business opportunities that may exist in a partnership, but more closely evaluate the clinical and scientific aspects of their offering and the science behind testing. For example, with some of the companies Nicole mentioned, and especially early on when we were meeting with the panel, a discussion and a point of conversation that came up quite frequently was, how do you really evaluate between the multiple options out there?

Because that's a huge challenge for clinicians: which one is the best? And why would I decide to send my test to this partner versus another partner? Or why would I choose this panel of tests versus that panel of tests, or what's different about this technology versus that technology? So, it's really important to dive a little bit deeper before we make those partner decisions as Nicole outlined so that the membership can feel confident in what we're bringing to them, not only from a business perspective, but I think most importantly, from a clinical and scientific perspective.

Nicole: I'll just add that some of these partners were legacy prior to us taking this investment in precision medicine. So, we have worked with those partners to bring them up to the quality standards the panel is looking for, and we've worked with them quite closely to do that Whether it's reducing turnaround time or improving their reporting, you know, we've really worked hand in hand with them to bring them up to the standard that we're looking for.

As we continue to innovate and advance in the precision medicine space, we will continue to keep our members informed and up to date. As always, we remain dedicated to your practice success. To learn more about our Precision Medicine Center, visit: iononline.com/precision-medicine-center

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Consider GILOTRIF as early as second-line for patients with metastatic squamous NSCLC who progressed after platinum-based chemotherapy[1,2]

INDICATIONS AND USAGE

- **GILOTRIF is indicated for** the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Diarrhea

- GILOTRIF can cause diarrhea which may be severe and can result in dehydration with or without renal impairment. In clinical studies, some of these cases were fatal.
- For patients who develop Grade 2 diarrhea lasting more than 48 hours or Grade 3 or greater diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and then resume at a reduced dose.
- Provide patients with an anti-diarrheal agent (e.g., loperamide) for self-administration at the onset of diarrhea and instruct patients to continue anti-diarrheal until loose stools cease for 12 hours.

Bullous and Exfoliative Skin Disorders

- GILOTRIF can result in cutaneous reactions consisting of rash, erythema, and acneiform rash. In addition, palmar-plantar erythrodysesthesia syndrome was observed in clinical trials in patients taking GILOTRIF.
- Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating skin lesions. For patients who develop Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF. When the adverse reaction resolves to Grade 1 or less, resume GILOTRIF with appropriate dose reduction.
- Postmarketing cases of toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. Discontinue GILOTRIF if TEN or SJS is suspected.

Interstitial Lung Disease

- Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in patients receiving GILOTRIF in clinical trials. In some cases, ILD was fatal. The incidence of ILD appeared to be higher in Asian patients as compared to white patients.
- Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD.

Hepatic Toxicity

- Hepatic toxicity as evidenced by liver function tests abnormalities has been observed in patients taking GILOTRIF. In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal.
- Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function. Discontinue treatment in patients who develop severe hepatic impairment while taking GILOTRIF.

Gastrointestinal Perforation

- Gastrointestinal (GI) perforation, including fatal cases, has occurred with GILOTRIF. GI perforation has been reported in 0.2% of patients treated with GILOTRIF among 3213 patients across 17 randomized controlled clinical trials.
- Patients receiving concomitant corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or anti-angiogenic agents, or patients with increasing age or who have an underlying history of GI ulceration, underlying diverticular disease, or bowel metastases may be at an increased risk of perforation.
- Permanently discontinue GILOTRIF in patients who develop GI perforation.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.

GILOTRIF® (afatinib) tablets

Recommended dose[1]

- The recommended dose is 40 mg orally once daily
- In patients with pre-existing severe renal impairment, the recommended dose of GILOTRIF is 30 mg orally once daily*

How to take[1]

- Take GILOTRIF at least 1 hour before or 2 hours after a meal
- Do not take a missed dose within 12 hours of the next dose

Treatment duration[1]

- Treatment should be continued until disease progression or until no longer tolerated by the patient

Multiple strengths[1]

- Multiple tablet strengths are available for dose adjustment: 40 mg, 30 mg, and 20 mg

*Estimated glomerular filtration rate (eGFR) 15 to 29 mL/min/1.73 m^2.

WARNINGS AND PRECAUTIONS (cont'd)

Keratitis

- Keratitis has been reported in patients taking GILOTRIF.
- Withhold GILOTRIF during evaluation of patients with suspected keratitis. If diagnosis of ulcerative keratitis is confirmed, interrupt or discontinue GILOTRIF. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GILOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Embryo-Fetal Toxicity

- GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.
- Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF. Advise female patients to contact their healthcare provider with a known or suspected pregnancy.

ADVERSE REACTIONS

Adverse Reactions observed in clinical trials were as follows:

Previously Treated, Metastatic Squamous NSCLC

- In GILOTRIF-treated patients (n=392) the most common adverse reactions (≥20% all grades & vs erlotinib-treated patients (n=395)) were diarrhea (75% vs 41%), rash/acneiform dermatitis (70% vs 70%), stomatitis (30% vs 11%), decreased appetite (25% vs 26%), and nausea (21% vs 16%).
- Serious adverse reactions were reported in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

DRUG INTERACTIONS

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers

- Concomitant use of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib.
- Concomitant use of P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort) with GILOTRIF can decrease exposure to afatinib.

USE IN SPECIFIC POPULATIONS

Lactation

- Because of the potential for serious adverse reactions in breastfed infants from GILOTRIF, advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

- GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible.

Renal Impairment

- Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m^2 or who are on dialysis.

Hepatic Impairment

- GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated.

GF PROF ISI 10.21.19

References: 1. GILOTRIF [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **2.** Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol*. 2015;16(8):897-907.

Please see Brief Summary of Prescribing Information on the following pages.

Boehringer Ingelheim

GILOTRIF® (afatinib) tablets, for oral use

Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE: EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer: GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test. Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations. **Previously Treated, Metastatic Squamous NSCLC:** GILOTRIF is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Diarrhea: Diarrhea has resulted in dehydration with or without renal impairment across the clinical experience; some cases were fatal. Grade 3-4 diarrhea occurred in 697 (16%) of the 4257 patients who received GILOTRIF across 44 clinical trials. In LUX-Lung 3, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% were Grade 3 in severity and occurred within the first 6 weeks. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with GILOTRIF, of which 1.3% were Grade 3. In LUX-Lung 8, diarrhea occurred in 75% of patients treated with GILOTRIF (n=392), of which 10% were Grade 3 in severity and 0.8% were Grade 4 in severity. Renal impairment as a consequence of diarrhea occurred in 7% of patients treated with GILOTRIF, of which 2% were Grade 3 *[see Adverse Reactions]*. For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours, or greater than or equal to Grade 3 diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction. Provide patients with an anti-diarrheal agent (e.g., loperamide) for self-administration at the onset of diarrhea and instruct patients to continue anti-diarrheal therapy until loose bowel movements cease for 12 hours. **Bullous and Exfoliative Skin Disorders:** Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of the 4257 patients who received GILOTRIF across clinical trials. In LUX-Lung 3, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. In LUX-Lung 8, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 70%, and the incidence of Grade 3 cutaneous reactions was 7%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 1.5% *[see Adverse Reactions]*. Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF until the adverse reaction resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction. Postmarketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. The cases of TEN and SJS bullous skin reactions result from a distinct and separate mechanism of toxicity than the bullous skin lesions secondary to the pharmacologic action of the drug on the epidermal growth factor receptor. Discontinue GILOTRIF if TEN or SJS is suspected. **Interstitial Lung Disease (ILD):** Interstitial lung disease or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.6% of the 4257 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in Asian patients (2.3%; 38/1657) as compared to Whites (1.0%; 23/2241). In LUX-Lung 3, the incidence of Grade ≥3 ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients. In LUX-Lung 8, the incidence of Grade ≥3 ILD was 0.9% and resulted in death in 0.8% of GILOTRIF-treated patients. Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD. **Hepatic Toxicity:** In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal. In LUX-Lung 3, liver test abnormalities of any grade occurred in 17.5% of the patients treated with GILOTRIF, of which 3.5% had Grade 3-4 liver test abnormalities. In LUX-Lung 8, liver test abnormalities of any grade occurred in 6% of the patients treated with GILOTRIF, of which 0.2% had Grade 3-4 liver test abnormalities. Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function. In patients who develop severe hepatic impairment while taking GILOTRIF, treatment should be discontinued. **Gastrointestinal Perforation:** Gastrointestinal perforation, including fatal cases, has occurred with GILOTRIF. Gastrointestinal perforation has been reported in 0.2% of patients treated with GILOTRIF among 3213 patients across 17 randomized controlled clinical trials. Patients receiving concomitant corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) or anti-angiogenic agents, or patients with increasing age or who have an underlying history of gastrointestinal ulceration, underlying diverticular disease or bowel metastases may be at increased risk of perforation. Permanently discontinue GILOTRIF in patients who develop gastrointestinal perforation. **Keratitis:** Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with GILOTRIF among 4257 patients across clinical trials, of which 0.05% of patients experienced Grade 3 keratitis. Keratitis was reported in 2.2% patients in LUX-Lung 3, with Grade 3 in 0.4%. In LUX-Lung 8, keratitis was reported in 0.3% patients; there were no patients with ≥Grade 3 keratitis. Withhold GILOTRIF during evaluation of patients with suspected keratitis, and if diagnosis of ulcerative keratitis is confirmed, treatment with GILOTRIF should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GILOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye *[see Adverse Reactions]*. Contact lens use is also a risk factor for keratitis and ulceration. **Embryo-Fetal Toxicity:** Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF.

ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Diarrhea *[see Warnings and Precautions]*; Bullous and Exfoliative Skin Disorders *[see Warnings and Precautions]*; Interstitial Lung Disease *[see Warnings and Precautions]*; Hepatic Toxicity *[see Warnings and Precautions]*; Keratitis *[see Warnings and Precautions]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the Warnings and Precautions section reflect exposure to GILOTRIF for clinically significant adverse reactions in 4257 patients enrolled in LUX-Lung 3 (n=229) and LUX-Lung 8 (n=392), and 3636 patients with cancer enrolled in 42 studies of GILOTRIF administered alone or in combination with other anti-neoplastic drugs at GILOTRIF doses ranging from 10-70 mg daily or at doses 10-160 mg in other regimens. The mean exposure was 5.5 months. The population included patients with various cancers, the most common of which were NSCLC, breast, colorectal, brain, and head and neck. The data described below reflect exposure to GILOTRIF as a single agent in LUX-Lung 3, a randomized, active-controlled trial conducted in patients with EGFR mutation-positive, metastatic NSCLC, and in LUX-Lung 8, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy. EGFR Mutation-Positive, Metastatic NSCLC: The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naïve, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in a randomized, multicenter, open-label trial (LUX-Lung 3). Patients received GILOTRIF 40 mg daily until documented disease progression or intolerance to the therapy. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m^2 followed after 30 minutes by cisplatin 75 mg/m^2 every three weeks for a maximum of six treatment courses. The median exposure was 11 months for patients treated with GILOTRIF and 3.4 months for patients treated with pemetrexed/cisplatin. The overall trial population had a median age of 61 years; 61% of patients in the GILOTRIF arm and 60% of patients in the pemetrexed/cisplatin arm were younger than 65 years. A total of 64% of patients on GILOTRIF and 67% of pemetrexed/cisplatin patients were female. More than two-thirds of patients were from Asia (GILOTRIF 70%; pemetrexed/cisplatin 72%). Serious adverse reactions were reported in 29% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in GILOTRIF-treated patients in LUX-Lung 3 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%). Dose reductions due to adverse reactions were required in 57% of GILOTRIF-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%). Discontinuation of therapy in GILOTRIF-treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%). Clinical trials of GILOTRIF excluded patients with an abnormal left ventricular ejection fraction (LVEF), i.e., below the institutional lower limit of normal. In LUX-Lung 3, all patients were evaluated for LVEF at screening and every 9 weeks thereafter in the GILOTRIF-treated group and as needed in the pemetrexed/cisplatin group. More GILOTRIF-treated patients (2.2%; n=5) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%; n=1). Tables 1 and 2 summarize common adverse reactions and laboratory abnormalities in LUX-Lung 3.

Table 1 Adverse Reactions Reported in ≥10% of GILOTRIF-Treated Patients in LUX-Lung 3*

Adverse Reaction	GILOTRIF n=229		Pemetrexed/ Cisplatin n=111	
	All Grades (%)	Grade 3† (%)	All Grades (%)	Grade 3† (%)
Gastrointestinal disorders				
Diarrhea	96	15	23	2
Stomatitis[1]	71	9	15	1
Cheilitis	12	0	1	0
Skin and subcutaneous tissue disorders				
Rash/ acneiform dermatitis[2]	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections				
Paronychia[3]	58	11	0	0
Cystitis	13	1	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
Investigations				
Weight decreased	17	1	14	1
General disorders and administration site conditions				
Pyrexia	12	0	6	0
Eye disorders				
Conjunctivitis	11	0	3	0

*NCI CTCAE v 3.0

†None of the adverse reactions in this table except stomatitis (one patient on GILOTRIF [0.4%]) were Grade 4 in severity.

[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

[2]Includes acne, acne pustular, dermatitis, acneiform dermatitis, dermatosis, drug eruption, erythema, exfoliative rash, folliculitis, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin disorder, skin erosion, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer

[3]Includes paronychia, nail infection, nail bed infection

Other clinically important adverse reactions observed in patients treated with GILOTRIF but that occurred at a higher incidence in pemetrexed/cisplatin-treated patients and not listed elsewhere in section 6 include: decreased appetite (29% Grades 1-4, 4% Grade 3), nausea (25% Grades 1-4, 4% Grade 3), and vomiting (23% Grades 1-4, 4% Grade 3).

Table 2 Laboratory Abnormalities Occurring in ≥10% of GILOTRIF Arm and at ≥2% Higher Incidence than in Chemotherapy Arm in LUX-Lung 3*

Laboratory Abnormality	GILOTRIF n=229		Pemetrexed/ Cisplatin n=111	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alanine aminotransferase (ALT)	54	2	27	1
Increased alkaline phosphate	51	3	46	1
Decreased creatinine clearance	49	2	47	1
Increased aspartate aminotransferase (AST)	46	3	22	1
Decreased lymphocytes	38	9	32	14
Decreased potassium	30	8	11	3
Increased bilirubin	16	1	8	0

*NCI CTCAE v 3.0

Previously Treated, Metastatic Squamous NSCLC: The safety of GILOTRIF was evaluated in 392 GILOTRIF-treated patients with metastatic squamous NSCLC enrolled in a randomized, multicenter, open-label trial (LUX-Lung 8). Patients were required to have received at least four cycles of platinum-based chemotherapy, ECOG Performance Status (PS) 0 or 1, and normal left ventricular ejection fraction (LVEF). Patients received GILOTRIF 40 mg once daily (n=392) or erlotinib 150 mg once daily (n=395). Treatment continued until documented disease progression or intolerance to the therapy. Among the 392 GILOTRIF-treated patients, the median age was 65 years, 53% were 65 years of age or older, 84% were male, 72% were White, 25% were Asian, ECOG PS 0 (32%) or 1 (68%). The median exposure was 2.1 months for patients treated with GILOTRIF, 15% were exposed for at least 6 months, and 5% were exposed for at least 12 months. Serious adverse reactions occurred in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%). Dose reductions due to adverse reactions were required in 27% of GILOTRIF-treated patients and discontinuation of GILOTRIF for adverse reactions was required for 20%. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (15%), rash/acne (5.9%), and stomatitis (3.1%). The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (4.1%) and rash/acne (2.6%). Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in LUX-Lung 8.

Table 3 Adverse Reactions Reported in ≥10% of GILOTRIF-Treated Patients in LUX-Lung 8*

Adverse Reaction	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	75	11	41	3
Stomatitis[1]	30	4	11	1
Nausea	21	2	16	1
Vomiting	13	1	10	1
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis[2]	70	7	70	11
Pruritus	10	0	13	0
Infections				
Paronychia[3]	11	1	5	0
Metabolism and nutrition disorders				
Decreased appetite	25	3	26	2

*NCI CTCAE v 3.0

[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

[2]Includes acne, dermatitis, acneiform dermatitis, eczema, erythema, exfoliative rash, folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer

[3]Includes paronychia, nail infection, nail bed infection

Table 4 Laboratory Abnormalities Occurring in ≥10% of GILOTRIF Arm and at ≥2% Higher Incidence than in Erlotinib Arm in LUX-Lung 8*

Laboratory Abnormality	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphate	34	2	31	0
Decreased white blood cell count	12	1	8	1
Decreased potassium	11	1	8	1

*NCI CTCAE v 3.0

Other clinically important laboratory abnormalities observed in patients treated with GILOTRIF that are not listed in Table 4 are: increased alanine aminotransferase (10% Grade 1-4; 1% Grade 3-4), increased aspartate aminotransferase (7% Grade 1-4; 1% Grade 3-4), and increased bilirubin (3% Grade 1-4; 0 Grade 3-4). *Less Common Adverse Reactions:* Other adverse reactions reported in patients treated with GILOTRIF in LUX-Lung 3 and LUX-Lung 8 include: *Skin and subcutaneous disorders:* nail disorders occurred in 9.2% and 2.8% of patients, respectively. **Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of GILOTRIF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Pancreatitis; Toxic epidermal necrolysis/Stevens Johnson syndrome.

DRUG INTERACTIONS: *Effect of P-glycoprotein (P-gp) Inhibitors and Inducers:* Concomitant taking of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib. Concomitant taking of P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort) with GILOTRIF can decrease exposure to afatinib.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Risk Summary:* Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. There are no available data on the use of GILOTRIF in pregnant women. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages *[see Data]*. Advise a pregnant woman of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. *Data:* Animal Data: In an embryo-fetal development study in rabbits, administration of afatinib to pregnant animals at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater during the period of organogenesis caused increased post-implantation loss, and in animals showing maternal toxicity, abortion at late gestational stages. In the same study, at the high dose level of 10 mg/kg (approximately 0.7 times the exposure by AUC at the recommended human dose of 40 mg daily), there were reduced fetal weights, and increases in the incidence of runts, as well as visceral and dermal variations. In an embryo-fetal development study in rats, there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg (approximately twice the exposure based on AUC at the recommended human dose of 40 mg daily). **Lactation:** *Risk Summary:* There are no data on the presence of afatinib in human milk or its effects on the breastfed infant or on milk production. Afatinib was present in the milk of lactating rats *[see Data]*. Because of the potential for serious adverse reactions in nursing infants from GILOTRIF, advise a lactating woman not to breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose. *Data:* Afatinib was present in the milk of lactating rats at concentrations 80 and 150 times higher than those found in plasma at 1 and 6 hours after administration. **Females and Males of Reproductive Potential:** *Contraception:* Females: GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF, and for at least 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations]*. *Infertility:* Based on results from an animal fertility study, GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible. **Pediatric Use:** Safety and effectiveness of GILOTRIF in pediatric patients have not been established. **Geriatric Use:** LUX-Lung 3 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In LUX-Lung 8, 53% of the 398 patients randomized to receive afatinib were 65 years of age or older and 11% were 75 years or older. In an exploratory subgroup analysis of LUX-Lung 8, the hazard ratio for overall survival (OS) in patients less than 65 years old was 0.68 (95% CI: 0.55, 0.85) and in patients 65 years or older was 0.95 (95% CI: 0.76, 1.19). No overall differences in safety were observed between patients 65 years and older and younger patients. **Renal Impairment:** Patients with severe renal impairment have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild or moderate renal impairment. Dosing recommendations for patients with eGFR <15 mL/min/1.73 m^2 or on dialysis cannot be provided as GILOTRIF has not been studied in these patient populations. **Hepatic Impairment:** GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated.

OVERDOSAGE Overdose was reported in 2 healthy adolescents each of whom ingested 360 mg of GILOTRIF (as part of a mixed-drug ingestion) resulting in nausea, vomiting, asthenia, dizziness, headache, abdominal pain, and elevated amylase [<1.5 times upper limit of normal (ULN)]. Both subjects recovered.

PATIENT COUNSELING INFORMATION: *See FDA-approved patient labeling (Patient Information).* Diarrhea: Advise patients that diarrhea occurs in nearly all patients who receive GILOTRIF. Inform patients that diarrhea may result in dehydration and renal impairment if not treated. Advise patients to notify their physician if diarrhea develops and to seek medical attention promptly for severe or persistent diarrhea *[see Warnings and Precautions and Adverse Reactions]*. Bullous and Exfoliative Skin Disorders: Advise patients to minimize sun exposure with protective clothing and use of sunscreen while taking GILOTRIF *[see Warnings and Precautions]*. Interstitial Lung Disease: Advise patients to immediately report any new or worsening lung symptoms, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, fever *[see Warnings and Precautions]*. Hepatic Toxicity: Advise patients that they will need to undergo liver function monitoring periodically. Advise patients to immediately report any symptoms of a liver problem [e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleeds or bruises more easily than normal, lethargy] *[see Warnings and Precautions]*. Keratitis: Advise patients to immediately report eye problems (e.g., eye pain, swelling, redness, blurred vision, or other vision changes) *[see Warnings and Precautions]*. Left Ventricular Dysfunction: Advise patients to contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath or exercise intolerance, cough, fatigue, swelling of the ankles/legs, palpitations, or sudden weight gain *[see Adverse Reactions]*. Instructions for Taking GILOTRIF: Advise patients to take GILOTRIF on an empty stomach at least 1 hour before or 2 hours after eating. Advise patients not to take a missed dose within 12 hours of the next dose. Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential that GILOTRIF can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF and for at least 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations]*. Lactation: Advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations]*; Infertility: Advise females and males of reproductive potential of the potential for reduced fertility from GILOTRIF *[see Use in Specific Populations]*.

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Basics of biomarker testing

The human genome was mapped nearly two decades ago. Genomic testing technology is advancing and seems to be picking up speed every day.

"More than 300 gene-pair fusions in leukemias and solid tumors are included in the COSMIC (Catalogue of Somatic Mutations in Cancer) database."

The importance of the test results is also advancing, as the presence or absence of alterations—point mutations, amplifications, fusions, and many others—guides therapeutic strategies in this era of precision medicine.

In precision medicine, biomarker testing for individual patients is integral to multiple aspects of effective clinical decision-making. This process—sometimes termed genomic testing—identifies specific molecular alterations by determining the order of the nucleotides in the DNA or RNA strands. In oncology, biomarker tests are more often used to evaluate somatic (acquired) changes, as opposed to genetic tests that examine heritable germline mutations.

Rapid progress has been made since the first mapping of the human genome in the early 2000s. In many cancer types, clinical trials and treatment approaches that were centered around the tumor's location of origin are expanding to encompass the molecular profile.[1-3] The National Cancer Institute's Molecular Analysis for Therapy Choice (NCI-MATCH) Trial is an example of a phase 2 basket trial to study targeted therapies based on specific molecular alterations across a variety of tumor types—a concept known as tumor agnostic.[4] As more therapeutic targets are investigated and identified, expertise becomes not only more important but also more challenging.

Accurate interpretation and application of test results for individual patients informs the entire spectrum of treatment, often beginning at the time of initial diagnosis.[1,3,5] Genomic testing methods for biomarkers detect myriad somatic variations, including nucleotide insertions and deletions and gene fusions.

More than 300 gene-pair fusions in leukemias and solid tumors are included in the COSMIC (Catalogue of Somatic Mutations in Cancer) database.[6]

Gene fusions, which may result from chromosomal translocations, are the most common mutation class and contribute to as much as 20 percent of morbidity, depending on the type of cancer involved.[7,8] Detection of specific fusions plays an important role in diagnosis and treatment, as fusions are known to be oncogenic drivers across multiple hematologic malignancies and solid tumors.[9] The US Food and Drug Administration (FDA) has approved at least 12 single-agent therapies that target gene fusions in solid tumors and six in hematologic malignancies.[10,11] Not all genomic testing methods are efficient or effective for identifying fusions, however, and several individual biomarker testing methods may be available in any given clinical situation. In addition, combinations of tests could provide the most complete picture. To use the tests most effectively, providers need to have a clear understanding of what options are available as well as which are more suitable and the potential limitations of each.

Common testing approaches

Sanger sequencing

Sanger DNA sequencing, used in the Human Genome Project, was the first method developed for genomic testing. This test determines the nucleotide sequence in a DNA fragment—up to about 1,000 base pairs—around a known region.[12] It provides information on a limited range of mutations, such as substitutions and small insertions and deletions.[13]

Fluorescence in situ hybridization

A fluorescence in situ hybridization (FISH) test analyzes DNA to locate specific genes on the chromosome, determine how many copies are present, and identify such aberrations as translocations, amplifications, and deletions. RNA-based FISH may be used to detect expression of aberrant transcripts.[13,14] While this method can detect gene fusions, the process is often slow and iterative because each run typically identifies only one fusion gene. This approach is not scalable for testing multiple targets.[15] In addition, novel fusion partners and complex structural rearrangements cannot be detected, a limitation that had led to false-negative results in some hematologic cancers.[8] FISH can provide fast results for specific needs and be useful for validating the results of other methods.[2,15]

Polymerase chain reaction

Several types of polymerase chain reaction (PCR) tests are available, including reverse-transcription PCR (RT-PCR), anchored multiplex PCR (AMP), and quantitative PCR (qPCR).[2,15] All forms involve amplifying segments of DNA to facilitate analysis, especially in preparation for other tests.[2,16] RT-PCR can detect fusions if the RNA quality is high, but only when the fusion partner is known,[8] while AMP can be used when the partner is not known.[15] In general, PCR methods are low-throughput and provide limited resolution.[8]

Immunohistochemistry

Immunohistochemistry (IHC) is used to analyze small numbers of biomarkers to determine both the presence of proteins and their expression levels in a tumor.[13] Antibodies labeled with enzymes or fluorescent dye are mixed with the sample and will bind to target antigens. The resulting report is based on the proportion of stained cells and the intensity of the staining. As a commonly available and sensitive test, IHC is often useful for screening patients to determine the need for other tests.

DNA microarray

The microarray method measures gene expression profiles of large numbers of genes simultaneously and can be used to genotype multiple genome regions.[2,17] The technique involves a premade library of synthetic nucleic acid probes that are immobilized and arrayed on a solid matrix.[18] Although microarray testing can provide information for diagnosis and prediction of treatment response, the measurement of gene expression may be limited by background at the low end and signal saturation at the high end.[5] For RNA, the method may have limited potential for detecting low-abundance or rare transcripts and identifying variants including fusions, nucleotide base modifications, transcript isoforms, and copy number changes.[2,19]

Next-generation sequencing

This high-throughput sequencing technology reveals a broad range of mutations through parallel sequencing of millions of fragments.[1,5,16,19] Next-generation sequencing (NGS) could include the whole genome (WGS) or be limited to selected areas, from whole exome sequencing (WES) down to individual genes.[1,2,13,20] While this technique is employed in the diagnosis and treatment of a variety of diseases, it is especially useful in oncology since cancer is a complex disease on a genetic level and additional actionable genomic changes are being elucidated on an ongoing basis. The breadth and depth of information provided by NGS could complement or even take the place of multiple single-gene testing methods while also gathering more information, including details on novel variants.[2]

NGS may analyze either DNA or RNA, and the methods for library preparation, target enrichment, and sequencing chemistry vary among alternatives.[19]

DNA sequencing

DNA sequencing can be used to detect driver and passenger mutations, copy number variants, rearrangements, and translocations, as well as to study gene expression.[3,5,20] WGS provides the most comprehensive information, but often WES or more narrowly targeted gene panels may be more expedient and less costly.[3,20] Many preselected panels are available commercially for more common or well-known genomic variants. The use of a gene panel could potentially provide more depth in the analysis since fewer genes are involved, but the narrower examination could also miss valuable information.[2,3]

Gene fusions are one critical class of somatic—and often actionable—driver mutations that may not be detected by many DNA sequencing methods,[2] especially if a hybrid capture method is used.[3,5] Even WES is likely to miss these alterations, because relevant somatic fusions are often located outside of coding regions.[2] Intronic regions may be extremely large and contain repetitive sequences, posing challenges for DNA-based sequencing.[22,23]

RNA sequencing

RNA sequencing (RNA-Seq) can analyze the entire transcriptome to provide information about gene fusions as well as expression, mutations, translocations, and transcript isoforms

and other variations.[3,5,19-21] The size of intronic regions is less of a concern with RNA-based approaches.[15]

Targeted RNA-Seq of 17,485 solid tumors identified NRG1 fusions in several KRAS wild-type invasive mucinous adenocarcinomas and a pancreatic adenocarcinoma that had not been detected by DNA NGS alone.[23,24] By examining the transcriptome, RNA-Seq provides more specific information about the actual proteins produced. Multiple fusion genes can be detected in one sample, including nucleotide-level resolution of fusion junctions.[8] RNA-Seq can be performed on the entire transcriptome or be targeted to improve turnaround time, reduce costs, and reduce the complexity of the data.[3,20]

As an NGS method, RNA-Seq is not limited to known variants; it can detect both novel fusions and fusion partners.[8,19] In a study that included 110 patients whose lung cancer was positive for NRG1 fusions, 18 different fusion partners were found, several of which had not been reported previously.[23]

RNA-Seq has a greater dynamic range for transcript expression, meaning that detection and quantification are reliable even at low expression levels.[19] Analysis of the transcriptome also enables a better understanding of the functional effects of mutations and other cancer-associated variations.[2] Noncoding RNA may also alter such molecular functions as transcription and translation regulation or lead to DNA methylation.[5,19,20] This information could have prognostic and pharmacogenomic implications, including potential development of resistance.[8] Understanding the transcriptome is important for understanding the connection between the genome and functional protein expression.[20]

Summary

Physicians must consider multiple factors when selecting among NGS, Sanger sequencing, FISH, PCR, IHC, or other methods for biomarker testing. The associated costs and turnaround times have to be balanced with the information that could potentially be provided by the results—much as each treatment must be carefully balanced between benefits and drawbacks—all while considering the complexity of individual patient tumors.

Sanger sequencing

- DNA fragments
- Useful with low number of samples
- Provides limited information about mutations

FISH

- DNA and RNA
- Translocations, amplifications, and deletions
- Matches only exact changes and known fusion partners, one gene at a time
- Not useful for high-volume targeting

RT-PCR

- DNA and RNA
- Amplifies small segments and may be used to prepare samples for further tests
- Matches only exact changes and known fusion partners

IHC

- Proteins and protein expression
- Analyzes small number of biomarkers
- Useful to screen for further testing

Microarray

- Gene expression
- Can analyse large numbers of genes simultaneously
- May not identify all transcripts or differentiate isoforms

NGS DNA

- Whole genome, whole exome, or targeted panels
- More comprehensive coverage of driver and passenger mutations and multiple types of alterations
- No detection of trascriptions
- Read length limitations

NGS RNA

- Whole transcriptome or targeted panels
- Detects fusions, including novel fusions
- Novel genes and chimeric transcripts, alternative splice variants
- Identifies fusion proteins and functional effects of variations
- Analyzes only expressed genes

Abbreviations

- FISH: fluorescence insitu hybridization
- PCR: polymerase chain reaction
- IHC: immunohistochemistry
- NGS: next-generation sequencing

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Government affairs Q&A

By Rita Norton
Senior Vice President, Government and Public Policy

The dangers of potential Medicare cuts and what practices can expect in 2022

Rita Norton walks us through potential reimbursement challenges, suggests a path for advocacy, and shares her expert opinion on what specialty physician practices will face next year, absent Congressional action.

As 2021 comes to a close, we sat down with Rita Norton, Senior Vice President, Government and Public Policy, for a discussion on a pending uphill battle for physician practices.

Can you walk us through the concern around potential Medicare cuts?
Rita Norton: The cuts to monitor as we move into 2022 are actually three distinct parts. First, Medicare sequestration relief is once again scheduled to expire. As our practices remember, Congress temporarily delayed cuts to sequestration in 2020 and 2021, giving providers an extra financial boost during the pandemic. The clock on that most recent delay runs out March 31, 2022 and the end result will be a 2 percent cut to Medicare reimbursement rates. This would be followed by a reinstated 1 percent reduction in payment through June 30, 2022. Without further action, the 2 percent cut would return on July 1, 2022.

Second, Congress enacted a temporary 3.75 percent increase in physician's Medicare pay. Initially, this one-time increase was designed to help providers offset the cuts triggered by the 2021 Medicare Physician Fee Schedule Final Rule. Recent legislation kept this in place, but adjusted the Physician Fee Schedule to 3 percent for calendar year 2022.

Third, Congress did not fully offset the costs of the American Rescue Plan Act, which set off budget rules known as "PAYGO." Simply put, automatic Medicare sequestration is triggered when legislation is not passed in a deficit neutral way. This would create an addition 4 percent sequester rate, but recent legislation delayed the statutory PAYGO cuts to Medicare until 2023. The expectation is that this will be revisited in early 2022.

What other cuts influence our specialties could be coming down the pipeline?
Rita: Well, consider the temporary percent rate increase. If it expires, the Centers for Medicare & Medicaid Services will take that expiration into account when determining the conversion factor. That's just a fancy way of saying reimbursement would be lowered by 3 percent.

After a two-year delay, CMS finalized the majority of the proposed revisions to the mandatory Radiation Oncology Model (ROM) in the final 2022 OPPS/ASC rule. The model will begin January 1, 2022, and end in December 2026. The ROM is complex, requiring practices to submit quality measures and clinical data elements. It has the potential to lower physician reimbursement rates and creates uncertainties that may negatively impact providers and patients. This model would change the way radiation services are paid—from fee-for-service payments to site neutral, modality agnostic, episode payments—with a goal of seeing if such changes incentivize physicians to deliver higher value care.

However, under the ROM, Medicare payment rates for radiation oncology services for certain cancers would decrease—a 13 percent drop for breast and colon cancer treatments and a 22 percent drop for advanced lung cancer treatments. The five-year model is scheduled to start on January 1, 2022. AmerisourceBergen has joined with other organizations, such as ASTRO and the Community Oncology Alliance in filing public comments opposing much of CMS' proposed rule. While the implementation had been delayed for one year, and CMS had made some adjustments, they did not go far enough. AmerisourceBergen, though our Specialty Physician Services business unit, advocated for a positive conversion factor and at least delaying implementation of the ROM for a year to provide time to enact reforms that would extend CMS' revisions.

Why should our practices be worried?
Rita: One of the easiest ways for the government to save money in healthcare is to lower the amount they reimburse providers. Many of our physician practices are reimbursed through Medicare Part B and that's always the biggest target.
We're just starting to turn the corner after the pandemic. Such cuts could be devastating to our practices' viability. In the 2021 Survey of America's Physicians by the Physicians Foundation, 68 percent of independent physicians across all specialties reported a decrease in their income.

Our fear is that physician practices may not be able to keep their doors open and serve their patients, many of whom rely on the care they provide in rural and underserved areas.

What advocacy steps are AmerisourceBergen taking?
Rita: Through Community Counts, we are urging our members to contact their U.S. senators and representatives. We know our practices are highly politically engaged and Community Counts is an effective platform for them to reach their elected officials.

Our specialty physician practice community has embraced these types of action alerts before. For example, one successful Community Counts action campaign was when the sequestration relief was set to expire. Through our grassroots efforts, 1500 letters were sent to 271 legislators. Those letters outlined the very real impacts these cuts would have had on specialty physicians' livelihoods and

ability to provide the highest standards of care. The Senate passed, and the president signed into law, a bill extending the Medicare Part B sequestration moratorium. Such advocacy efforts prove the power of providers speaking out for themselves.

Where are we with drug pricing reform?

Rita: This is a consistently an important issue. Lowering drug prices remains a very popular idea among Americans across the political spectrum.

In early November, Congressional Democrats announced a deal to lower prescription drug pricing. It gives Medicare the ability to negotiate prices on drugs that are older — 9 years for orals and 13 years for biologics. The plan also would cap senior citizens out-of-pocket (OOP) costs, place a $35/month OOP cap on insulin products, and force pharmaceutical manufactures to pay penalties if they raise prices faster than inflation rates.

Of course, a deal is not a law. If the House passes this legislation it will undergo changes in the Senate — likely in December. President Biden has expressed his support, but it still needs to pass through both houses of Congress before it hits his desk.

Is there other pending legislation with the potential to affect specialty physician practices?

Two items of interest are the end of the COVID-19 Public Health Emergency (PHE) and the end of Medicare telehealth flexibilities.

CMS put telehealth flexibilities and increased Medicare reimbursements in place to address restrictions from the pandemic. These new provisions widened patients' access to care and providers' reimbursement for that care. Patients can have their initial telehealth consultation from their home, where previously, they had travel to the doctor's office, clinic, or hospital. Telehealth's reach was expanded to urban, suburban, and rural areas and coverage for home health and remote patient monitoring was expanded.

These and other provisions are set to expire at the end of January when the PHE expires. The Biden administration is expected to extend the PHE for another year, although, as we know, there are no guarantees in politics.

The 2022 Medicare Physician Fee Schedule did extend some of the telehealth provisions, regardless of whether or not the Public Health Emergency continues. Various physician advocacy groups have lobbied Congress to take up legislation to permanently change extend the flexibilities.

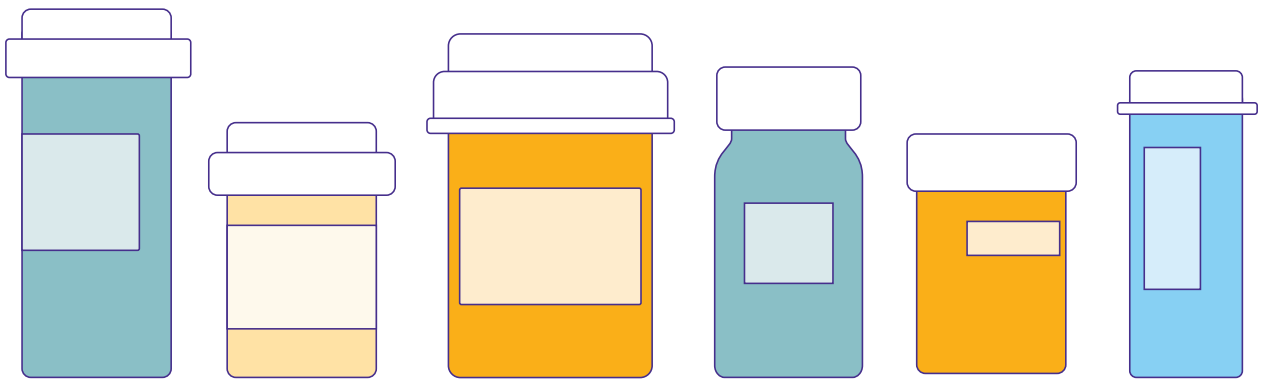
What else should specialty practices be on the lookout for in 2022?

Pharmacy benefit manager reforms are a consistent issue for community practices. Six groups, including the Community Oncology Alliance and the Council of State Rheumatology Organizations, have formed the Coalition for PBM Reform. The coalition wants to address the lack of PBM transparency that can impact provider decision making and patient access.

PBM reform goes beyond the grassroots level. Senate Finance Committee Chairman Ron Wyden (D-OR) has sent a letter to CMS urging them to take on PBM reforms. In the state houses, various legislative efforts to curb PBM's reach are currently under consideration.

We look forward to continuing to partner with physicians to try and stop these steep, scheduled Medicare physician fee cuts, and on structural healthcare reforms.

To get involved, visit Community Counts: communitycountsadvocacy.org



RELISTOR injection is the only treatment approved for opioid induced constipation (OIC) available to eligible members through your ION GPO contract

RELISTOR Injection is the only treatment indicated for OIC in adults with advanced illness or active cancer pain*

***Who require opioid dosage escalation for palliative care.[1]**

Learn more at RELISTORhcp.com

INDICATIONS

- RELISTOR® (methylnaltrexone bromide) is an opioid antagonist. RELISTOR subcutaneous injection is indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.
- RELISTOR injection is also indicated for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.

IMPORTANT SAFETY INFORMATION

- RELISTOR injection is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation.

Please see Brief Summary of full Prescribing Information for RELISTOR following this advertisement.

IMPORTANT SAFETY INFORMATION (Continued)

- Cases of gastrointestinal perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR injection in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue RELISTOR injection in patients who develop this symptom.
- If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR injection and consult their healthcare provider.
- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR injection. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia and should be monitored for adequacy of analgesia and symptoms of opioid withdrawal.
- In a clinical study, the most common adverse reactions for RELISTOR injection (≥ 1% of RELISTOR patients and at a greater incidence than placebo) in adult patients with chronic non-cancer pain were: abdominal pain (21%), nausea (9%), diarrhea (6%), hyperhidrosis (6%), hot flush (3%), tremor (1%), and chills (1%).
- In clinical studies, the most common adverse reactions for RELISTOR injection (≥ 5% of RELISTOR patients and at a greater incidence than placebo) in adult patients with advanced illness were: abdominal pain (29%), flatulence (13%), nausea (12%), dizziness (7%), and diarrhea (6%).
- Avoid concomitant use of RELISTOR injection with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.
- The use of RELISTOR injection during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. Advise pregnant women of the potential risk to a fetus. Because of the potential for serious adverse reactions, including opioid withdrawal, in breastfed infants, advise women that breastfeeding is not recommended during treatment with RELISTOR injection.
- A dosage reduction of RELISTOR injection is recommended in patients with moderate and severe renal impairment (creatinine clearance less than 60 mL/minute as estimated by Cockcroft-Gault). No dosage adjustment of RELISTOR injection is needed in patients with mild renal impairment.
- No dosage adjustment of RELISTOR injection is needed for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, monitor for methylnaltrexone-related adverse reactions and dose adjust per Prescribing Information as may be indicated.

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information for RELISTOR following this advertisement.

REFERENCES: 1. RELISTOR [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals.

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RELISTOR®
methylnaltrexone bromide
Subcutaneous Injection

RELISTOR® *methylnaltrexone bromide* Subcutaneous Injection **RELISTOR®** *methylnaltrexone bromide* Tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use RELISTOR safely and effectively. See full prescribing information for RELISTOR.

RELISTOR (methylnaltrexone bromide) 150 mg tablets, for oral use.

RELISTOR (methylnaltrexone bromide) injection, for subcutaneous use.

8 mg/0.4 mL methylnaltrexone bromide in single-dose pre-filled syringe. 12 mg/0.6 mL methylnaltrexone bromide in a single-dose pre-filled syringe, or single-dose vial. **Initial U.S. Approval: 2008**

1 INDICATIONS AND USAGE

1.1 Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain RELISTOR tablets and RELISTOR injection are indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

1.2 Opioid-Induced Constipation in Adult Patients with Advanced Illness RELISTOR injection is indicated for the treatment of OIC in adult patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.

4 CONTRAINDICATIONS

RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforation Cases of gastrointestinal perforation have been reported in adult patients with OIC and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue RELISTOR in patients who develop this symptom *[see Contraindications (4)]*.

5.2 Severe or Persistent Diarrhea If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their healthcare provider.

5.3 Opioid Withdrawal Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR *[see Adverse Reactions (6.1)]*. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. Take into account the overall risk-benefit profile when using RELISTOR in such patients. Monitor for adequacy of analgesia and symptoms of opioid withdrawal in such patients.

6 ADVERSE REACTIONS

Serious and important adverse reactions described elsewhere in the labeling include:

- Gastrointestinal perforation *[see Warnings and Precautions (5.1)]*
- Severe or persistent diarrhea *[see Warnings and Precautions (5.2)]*
- Opioid withdrawal *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

The safety of RELISTOR tablets was evaluated in a double-blind, placebo-controlled trial in adult patients with OIC and chronic non-cancer pain receiving opioid analgesia. This study (Study 1) included a 12-week, double-blind, placebo-controlled period in which adult patients were randomized to receive RELISTOR tablets 450 mg orally (200 patients) or placebo (201 patients) *[see Clinical Studies (14.1)]*. After 4 weeks of double-blind treatment administered once daily, patients continued 8 weeks of double-blind treatment on an as needed basis (but not more than once daily).

The most common adverse reactions in adult patients with OIC and chronic non-cancer pain receiving RELISTOR tablets are shown in **Table 4**. Adverse reactions of abdominal pain, diarrhea, hyperhidrosis, anxiety, rhinorrhea, and chills may reflect symptoms of opioid withdrawal.

Table 4: Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR Tablets in Adult Patients with OIC and Chronic Non-Cancer Pain (Study 1)

Adverse Reaction	RELISTOR Tablets n = 200	Placebo n = 201
Abdominal Pain**	14%	10%
Diarrhea	5%	2%
Headache	4%	3%
Abdominal Distention	4%	2%
Vomiting	3%	2%
Hyperhidrosis	3%	1%
Anxiety	2%	1%
Muscle Spasms	2%	1%
Rhinorrhea	2%	1%
Chills	2%	0%

* Adverse reactions occurring in at least 2% of patients receiving RELISTOR tablets 450 mg once daily and at an incidence greater than placebo.

** Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness

The safety of RELISTOR injection was evaluated in a double-blind, placebo-controlled trial in adult patients with OIC and chronic non-cancer pain receiving opioid analgesia. This study (Study 2) included a 4-week, double-blind, placebo-controlled period in which adult patients were randomized to receive RELISTOR injection 12 mg subcutaneously once daily (150 patients) or placebo (162 patients) *[see Clinical Studies (14.1)]*. After 4 weeks of double-blind treatment, patients began an 8-week open-label treatment period during which RELISTOR injection 12 mg subcutaneously was administered less frequently than the recommended dosage regimen of 12 mg once daily.

The most common adverse reactions in adult patients with OIC and chronic non-cancer pain receiving RELISTOR injection are shown in **Table 5**. The adverse reactions in the table below may reflect symptoms of opioid withdrawal.

Table 5: Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR Injection in Adult Patients with OIC and Chronic Non-Cancer Pain (Study 2)

Adverse Reaction	RELISTOR Injection n = 150	Placebo n = 162
Abdominal Pain**	21%	7%
Nausea	9%	6%
Diarrhea	6%	4%
Hyperhidrosis	6%	1%
Hot Flush	3%	2%
Tremor	1%	<1%
Chills	1%	0%

* Adverse reactions occurring in at least 1% of patients receiving RELISTOR injection 12 mg subcutaneously once daily and at an incidence greater than placebo.

** Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness

During the 4-week double-blind period, in patients with OIC and chronic non-cancer pain that received RELISTOR every other day, there was a higher incidence of adverse reactions, including nausea (12%), diarrhea (12%), vomiting (7%), tremor (3%), feeling of body temperature change (3%), piloerection (3%), and chills (2%) as compared to daily RELISTOR dosing. Use of RELISTOR injection 12 mg subcutaneously every other day is not recommended in patients with OIC and chronic non-cancer pain *[see Dosage and Administration (2.2)]*. The rates of discontinuation due to adverse reactions during the double-blind period (Study 2) were higher in the RELISTOR once daily (7%) than the placebo group (3%). Abdominal pain was the most common adverse reaction resulting in discontinuation from the double-blind period in the RELISTOR once daily group (2%).

The safety of RELISTOR injection was also evaluated in a 48-week, open-label, uncontrolled trial in 1034 adult patients with OIC and chronic non-cancer pain (Study 3). Patients were allowed to administer RELISTOR injection 12 mg subcutaneously less frequently than the recommended dosage regimen of 12 mg once daily, and took a median of 6 doses per week. A total of 624 patients (60%) completed at least 24 weeks of treatment and 477 (46%) completed the 48-week study. The adverse reactions seen in this study were similar to those observed during the 4-week double-blind period of Study 2. Additionally, in Study 3, investigators reported 4 myocardial infarctions (1 fatal), 1 stroke (fatal), 1 fatal cardiac arrest and 1 sudden death. It is not possible to establish a relationship between these events and RELISTOR.

Opioid-Induced Constipation in Adult Patients with Advanced Illness

The safety of RELISTOR injection was evaluated in two, double-blind, placebo-controlled trials in adult patients with OIC and advanced illness receiving palliative care: Study 4 included a single-dose, double-blind, placebo-controlled period, whereas Study 5 included a 14-day multiple dose, double-blind, placebo-controlled period *[see Clinical Studies (14.2)]*.

The most common adverse reactions in adult patients with OIC and advanced illness receiving RELISTOR injection are shown in **Table 6** below.

Table 6: Adverse Reactions from All Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR Injection in Adult Patients with OIC and Advanced Illness* (Studies 4 and 5)

Adverse Reaction	RELISTOR Injection n = 165	Placebo n = 123
Abdominal Pain**	29%	10%
Flatulence	13%	6%
Nausea	12%	5%
Dizziness	7%	2%
Diarrhea	6%	2%

* Adverse reactions occurring in at least 5% of patients receiving all doses of RELISTOR injection (0.075, 0.15, and 0.3 mg/kg) and at an incidence greater than placebo

** Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness

The rates of discontinuation due to adverse reactions during the double-blind, placebo-controlled clinical trials (Study 4 and Study 5) were comparable between RELISTOR (1%) and placebo (2%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of RELISTOR injection. Because reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Gastrointestinal Perforation, cramping, vomiting

General Disorders and Administration Site Disorders Diaphoresis, flushing, malaise, pain. Cases of opioid withdrawal have been reported *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 Other Opioid Antagonists Avoid concomitant use of RELISTOR with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.

7.2 Drugs Metabolized by Cytochrome P450 Isozymes

In healthy subjects, a subcutaneous dose of 0.3 mg/kg of RELISTOR did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy The use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Advise pregnant women of the potential risk to a fetus.

8.2 Lactation Because of the potential for serious adverse reactions, including opioid withdrawal, in breastfed infants, advise women that breastfeeding is not recommended during treatment with RELISTOR. In nursing mothers, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use Safety and effectiveness of RELISTOR tablets and injection have not been established in pediatric patients.

8.5 Geriatric Use Of the total number of patients in clinical studies of RELISTOR tablets, a total of 136 patients (10%) were aged 65 years and older, while 23 (2%) were aged 75 and older. In clinical studies of RELISTOR tablets, no overall differences in effectiveness were observed. Adverse reactions were similar; however, there was a higher incidence of diarrhea in elderly patients.

Of the total number of patients in clinical studies of RELISTOR injection, a total of 226 (28%) were aged 65 years and older, while 108 (13%) were aged 75 years and older. In clinical studies of RELISTOR injection, no overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Based on pharmacokinetic data, and safety and efficacy data from controlled clinical trials, no dosage adjustment based on age is recommended. Monitor elderly patients for adverse reactions.

8.6 Renal Impairment In a study of subjects with varying degrees of renal impairment receiving RELISTOR injection subcutaneously, there was a significant increase in the exposure to methylnaltrexone in subjects with moderate and severe renal impairment (creatinine clearance less than 60 mL/minute as estimated by Cockcroft-Gault) compared to healthy subjects *[see Clinical Pharmacology (12.3)]*.

Therefore, a dosage reduction of RELISTOR tablets and RELISTOR injection is recommended in patients with moderate and severe renal impairment *[see Dosage and Administration (2.4)]*. No dosage adjustment of RELISTOR tablets or RELISTOR injection is needed in patients with mild renal impairment (creatinine clearance greater than 60 mL/minute as estimated by Cockcroft-Gault).

8.7 Hepatic Impairment *Tablets* In a study of subjects with varying degrees of hepatic impairment receiving a 450 mg dose of RELISTOR tablets, there was a significant increase in systemic exposure of methylnaltrexone for subjects with moderate (Child-Pugh Class B) and severe (ChildPugh Class C) hepatic impairment compared to healthy subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Therefore, a dosage reduction of RELISTOR tablets is recommended in patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.5)]*. No dosage adjustment of RELISTOR tablets is needed in patients with mild hepatic impairment (Child-Pugh Class A).

Injection In a study of subjects with mild or moderate hepatic impairment, there was no clinically meaningful change in systemic exposure of methylnaltrexone compared to healthy subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Therefore, no dosage adjustment of RELISTOR injection is needed for patients with mild or moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*.

Patients with severe hepatic impairment were not studied. In patients with severe hepatic impairment, monitor for methylnaltrexone-related adverse reactions. If considering dosage adjustment, follow the recommendations in Table 3 *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

During clinical trials of RELISTOR administered orally and subcutaneously, one accidental case of methylnaltrexone bromide overdose was reported and no adverse events were reported as a result of the overdosage.

A study of healthy subjects noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus. Monitor for signs or symptoms of orthostatic hypotension and initiate treatment as appropriate.

If a patient on opioid therapy receives an overdose of RELISTOR, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis Oral administration of methylnaltrexone bromide at doses up to 200 mg/kg/day (about 81 times the subcutaneous maximum recommended human dose (MRHD) of 12 mg/day based on body surface area) in males and 400 mg/kg/day (about 162 times the subcutaneous MRHD of 12 mg/day) in females and in Sprague Dawley rats at oral doses up to 300 mg/kg/day (about 243 times the subcutaneous MRHD of 12 mg/day) for 104 weeks did not produce tumors in mice and rats.

Mutagenesis Methylnaltrexone bromide was negative in the Ames test, chromosome aberration tests in Chinese hamster ovary cells and human lymphocytes, in the mouse lymphoma cell forward mutation tests and in the in vivo mouse micronucleus test.

Impairment of Fertility Methylnaltrexone bromide at subcutaneous doses up to 150 mg/kg/day (about 122 times the subcutaneous MRHD of 12 mg/day; about 3.3 times the oral MRHD of 450 mg/day) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

In an in vitro human cardiac potassium ion channel (hERG) assay, methylnaltrexone caused concentration-dependent inhibition of hERG current (1%, 12%, 13% and 40% inhibition at 30, 100, 300 and 1000 micromolar concentrations, respectively).

For more information, go to www.Relistor.com or call 1-800-321-4576.

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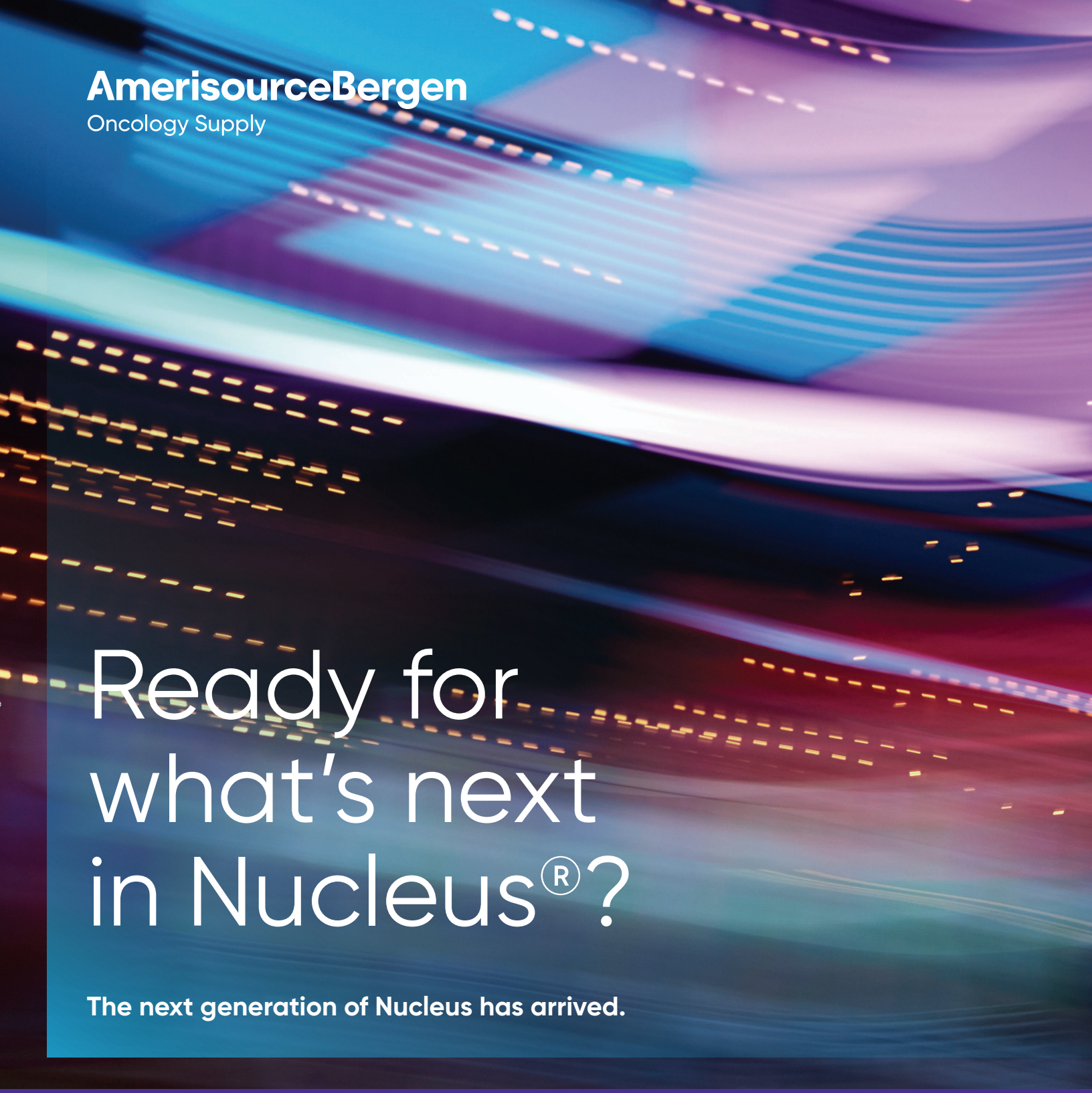

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Welcome to
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2021

Eye on ION

Return to live programming with ION National

This Fall, ION returned to live educational programming with its 2021 National Conference. ION members were invited to the event in Plano, Texas for a full day of content. The conference was divided into clinical and business tracks, with presentations geared toward physicians, nurses, pharmacists, nurse practitioners, physician assistants, practice managers, and CEOs.

In the clinical track, a number of key opinion leaders across multiple tumor types delivered the most recent scientific updates and findings.

Tanios Bekaii-Saab, MD, presented on GI Cancers; William Blum, MD, delivered a talk on Myeloid Malignancies; Eleni Efstathiou, MD, covered GU Cancers; Patrick Forde, MD, presented Lung Cancer; Filipa Lynce, MD, discussed Breast Cancer; and Deb Armstrong, MD closed out the session with GYN Cancers.

In the business track, operational, financial, and legislative topics were covered.

Attendees heard about innovation services that their peers have implemented to enhance patient care: Justin Rousek and Tracy Bender from Cancer Partners of Nebraska discussed how they implemented occupational therapy into their practice's offerings.

Landscape-altering ideas and strategies were introduced for consideration: Kashyap Patel, MD, discussed how the healthcare industry — providers, manufacturers, GPOs, pharmacies, and others — address disparities in cancer care.

Ideas, services, and topics that will greatly impact the level, quality, and comprehensiveness of patient care in the community session were discussed throughout the day: Susan Weidner presented on the future of targeted therapies; Christie Smith highlighted new payer models for medically integrated dispensing; and Fred Ashbury talked about the need for AI decision support in medicine.

A number of the presentations were recorded and are available on iononline.com. If you have any questions about this program, or are interested in attending a future ION event, please contact your ION strategic account manager.

ION OnCall

ION OnCall is a podcast series from AmerisourceBergen where we discuss the latest industry information relevant to our GPO member practices. In this series, we share regular updates from our knowledgeable staff and partners, as well as your respected peers, on everything from precision medicine and biosimilar innovations to practice management solutions and the legislative landscape. Listen from your computer during breaks at the office or from your phone on the go—we make it easy to fit educational content into your schedule. Subscribe today at oncall.buzzsprout.com

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