Test adds twists to lung disease diagnosis

Karen Titus

November 2023—It was a mystery, wrapped less in an enigma than a few layers of bafflement, surprise, and mild irritation. Call it the Case of the Split Lung Specimens.

The first hint something was amiss came when Alain Borczuk, MD, vice chair of anatomic pathology and co-director of thoracic pathology, Northwell Health, noticed that he and his colleagues were receiving more insufficient bronchoscopy specimens than usual. “When I say ‘increasing’—we don’t get that many bronchoscopies. It’s not like colon polyps,” says Dr. Borczuk, who is also director of oncologic pathology, Northwell Health Cancer Institute. Normally they would get a handful a week, some of them straightforward cancer cases, although these additional cases were tied to noncancerous conditions.

And then the plot thickened even further, with missing pieces—literally.

Though no guideline clearly states what constitutes an adequate specimen, Dr. Borczuk says, the samples he and his colleagues were seeing fell markedly short. In looking for a disease that involves the alveoli, rather than just the airway, one would expect at least two pieces to contain alveolar lung parenchyma, he says.

Instead, they were seeing two pieces of airway wall alone or very minimal amounts of alveolar lung parenchyma. It was unusual, to say the least. “I just hadn’t been in a situation where I had to state, in so many cases, that there were limited number of alveoli.” He says he prefers not to report such cases as inadequate sampling of the lung, given its inexact definition. But faced with this uptick in limited samples, he and his colleagues found themselves regularly debating whether to use that term.

And then a breakthrough occurred: In a multidisciplinary conference, it came to light that clinicians were splitting up the samples, sending some to the lab for traditional tissue biopsy and the rest to Veracyte, to be analyzed with the company’s Envisia Genomic Classifier.

The classifier aims to identify usual interstitial pneumonia (UIP) molecular pattern. This defining morphology of idiopathic pulmonary fibrosis, a chronic and progressive interstitial lung disease, is often identified by high-resolution CT within the appropriate clinical context. In cases that are not definitive, histology can help with the diagnosis.

The Envisia test represents a different approach. The biomarker makes a binary distinction between UIP/non-UIP in transbronchial lung biopsy samples, using a 190-gene machine learning classifier (Lasky JA, et al. *Ann Am Thorac Soc.* 2022;19[6]:916–924; Richeldi L, et al. *Am J Respir Crit Care Med.* 2021;203[2]:211–220).

Some pulmonologists are using a genomic classifier as an aid in identifying usual interstitial pneumonia molecular pattern to facilitate a diagnosis of idiopathic pulmonary fibrosis. At National Jewish Health, says Dr. Steve Groshong, chief of pathology, pulmonologists use it only in certain circumstances. [Photo by Barry Staver]

Dr. Borczuk recalls how he learned where the samples were disappearing to. The case in question involved an extremely small sample that was being considered for an alternative diagnosis. His pulmonologist colleague, Arunabh Talwar, MD, noted Dr. Borczuk's report mentioned the presence of a granuloma. But the sample was so small, Dr. Borczuk conceded to Dr. Talwar, "that the only reason I mentioned one tiny granuloma was it was the only thing there I could actually comment on."

Dr. Talwar then told him, "The Envisia test says it's IPF."

Dr. Borczuk was startled. "I said, 'What Envisia test?'"

That tiny sample led to sizable conversations at Northwell. Dr. Borczuk and other experts say such conversations will need to become de rigueur elsewhere as well (if they're not already) as pathologists help their clinical colleagues decide whether and how to pivot (if they haven't already) to Envisia.

The emergence of the classifier has also reinvigorated concerns about long-standing limitations in diagnosing UIP and other fibrotic interstitial lung diseases. If new methods such as a genomic classifier cause frustration, so do the approaches that came into being decades ago.

"The fundamental problem," says Jeffrey Myers, MD, "is being able to classify diffuse parenchymal lung diseases using anything short of surgical lung biopsy." Dr. Myers is the A. James French professor of pathology and vice

chair, clinical affairs and quality, Michigan Medicine.

“Everyone wants a magical test,” adds Viera Lakticova, MD, director of interventional pulmonology and bronchoscopy, Lenox Hill Hospital, and assistant professor of medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell.

Of course they do. UIP is one of the more complex areas in pulmonary pathology. It’s not limited to idiopathic pulmonary fibrosis, and cases are less common than asthma or COPD. Wedge biopsies can provide useful information, but not every patient is a good candidate.

Conventional transbronchial lung biopsies are less invasive, but not completely so, and the yield (four to six pieces, usually 2-mm to 3-mm “pinches” of tissue) can be insufficient to make the diagnosis, versus the more generous samples from surgical lung biopsy, which are typically 3 cm or 4 cm by 2 cm, from each of the three lobes on the right side. “That turns into seven or eight slides full of tissue,” says Steve Groshong, MD, PhD, chief of pathology and medical director of clinical laboratories, National Jewish Health, Denver. Cryobiopsy, a more recently developed technique, has its own limitations.

It’s not surprising, then, that the arrival of a genomic classifier has turned heads.

Dr. Groshong was involved in the BRAVE study of the test; he, along with several pulmonary and radiology colleagues at National Jewish Health, served as one of the core reading facilities of sorts to provide centralized review (Raghu G, et al. *Lancet Respir Med.* 2019;7[6]:487–496).

Given his involvement, he purposely recused himself from discussions about whether to use the Envisia Genomic Classifier at the institution. “But what kind of naturally evolved is that many of our ILD docs started using it.” The data they gleaned from the test, he says, matched their clinical expectations. “So they started to believe in it, in a sense.” They now use it fairly frequently, he says, though only in certain circumstances.

Dr. Groshong explains: If, for example, a patient is age 75 or older—an age at which IPF would be a reasonable diagnosis—and the CT scan shows the classic UIP pattern of honeycombing, “we usually just stop there.” No biopsy is needed.

Those who are candidates for biopsy include patients with unusual histories: too young to have IPF, for example, or a nondiagnostic CT pattern, such as honeycombing in the upper lobe rather than the lower lobe, or absence of honeycombing despite the presence of fibrosis. If the patient is young and otherwise healthy, they would be a good candidate for a wedge biopsy, says Dr. Groshong. Otherwise, a transbronchial biopsy with Envisia makes sense.

“For our docs, anyway, they always trust the wedge biopsy more,” says Dr. Groshong, “but a lot of times it’s not an option—the patient can’t tolerate a surgical procedure like that, or they cannot afford to lose more lung function in a large biopsy.”

Against that broader background, Dr. Groshong says, some pulmonologists use Envisia frequently; others, less so. “But for most of those cases, honestly, in pathology we’re never even aware they happen. We get the transbronchs just to read out for disease and make sure there aren’t granulomas and do AFB/GMS stains—that sort of thing. But the fragments they took for the classifier usually get packed up in the procedure room and shipped off, so we’re not directly aware of those until after the fact.”

No doubt that sounds familiar to Dr. Borczuk.

He was not involved in Envisia studies and doesn’t advocate for or against the test. “I’m more focused on the practical problem of integrating the test” into clinical practice.

After learning that Envisia was being used at Northwell, he and his pathologist colleagues looked into the details of the case in question. As it turns out, he says, “It didn’t really fit the indication for the test.”

Dr. Borczuk

The intent of transbronchial biopsies, Dr. Borczuk explains, was never to diagnose lung fibrosis; rather, it's to identify an alternative diagnosis. If the radiology was suggestive of a fibrotic lung process, then the decision would be made to treat the patient based on the radiology, or, alternatively, if it were still ambiguous, to do some type of wedge biopsy. Definite cases of UIP require no tissue sampling.

In the category where alternative diagnosis is the primary designation for radiology, Dr. Borczuk continues, "The Envisia test is really not appropriate," since it provides a binary answer. "But the pretest probability of the alternative diagnosis in that group is much higher, and the transbronchial biopsy is what's going to give you [that] insight."

That was made harder by the errant journeys the samples were taking at Northwell and beyond. If, say, six pieces of tissue were obtained by the bronchoscopy, three were sent for Envisia testing and three for pathology. "You've just reduced your chance of making the alternative diagnosis by half," Dr. Borczuk says.

Dr. Borczuk told his clinical colleagues that if they were going to send transbronchial biopsy samples for Envisia testing, "I don't want anything sent to pathology." After all, he reminded them, "The indication for Envisia is to answer a diagnosis that I cannot answer through transbronchial biopsy. And therefore I don't need one."

After smoothing ruffled feathers—in part to clarify that he wasn't criticizing bronchoscopists' techniques per se—"We all had a good conversation that led to the desire to create an algorithm," a four-step process for fibrotic lung disease to make clear across the system when the Envisia test is most likely to be useful.

As Dr. Borczuk explains, the first step recognizes the presence of a fibrotic lung disease that's associated with a known clinical diagnosis, such as sarcoidosis or a drug-induced or occupational disease. In that setting, a tissue biopsy is likely not needed. "And it will be left to the clinician as to whether they want any kind of test."

"Step two is that it's possibly hypersensitivity pneumonitis," he continues. This will entail a lavage, and maybe a transbronchial biopsy, but no Envisia test. "They could also opt for a surgical biopsy, but that's a different discussion."

In step three, the question is whether the CT shows UIP or probable UIP. Tissue sampling is not required in most cases.

Step four involves an indeterminate UIP pattern. In that setting, says Dr. Borczuk, the idiopathic pulmonary fibrosis or the UIP is only about a 50 percent pretest possibility. A surgical biopsy would be offered, but in cases where it's considered too risky or the patient declines, then a transbronchial biopsy would be performed, with or without Envisia. If it's felt a larger piece of tissue is needed, then a cryobiopsy would be performed. While the cryobiopsy does provide more tissue, Envisia does not accept these specimens, Dr. Borczuk notes.

The last part of this step, he says, is that if it is in fact an alternative diagnosis, and given that Envisia addresses only the UIP/non-UIP question, if UIP/IPF is less than 25 percent likely, then a transbronchial biopsy—or a cryobiopsy if possible—would be performed, but Envisia would not.

In short, he says, the algorithm suggests using Envisia only in cases where the UIP pattern is indeterminate. This has ended the problem of splitting samples.

"This narrowed the scope," Dr. Borczuk says. Since adopting the algorithm, "We've been getting more cryobiopsies in the alternative diagnoses category." If Envisia is being used in cases in which transbronchial biopsies aren't all

that helpful, “I wouldn’t know about it again—because no one’s talking to me about Envisia results.”

In that sense, he’s come full circle since he first learned of Envisia’s use at Northwell. “But I haven’t seen the problem of inadequate biopsies since.”

Dr. Lakticova, the interventional pulmonologist at Northwell, found herself beleaguered by small samples as well, though from a different angle.

Interstitial lung disease with UIP pattern is difficult to diagnose on conventional transbronchial biopsy, she notes. “And when we perform them, the amount of tissue we are getting is frequently insufficient to make the call.”

When neither cryobiopsy nor surgical lung biopsy is an option, they’ll turn to the Envisia Genomic Classifier. A positive test lets physicians know the patient has the UIP signal, which can indicate either IPF or another disease with UIP pattern, she says. “If the test is negative, it does not mean the diagnosis is not present. It just means we may be missing it.”

It’s a slender path. “I think the utility of the test is to help in the diagnosis of idiopathic pulmonary fibrosis, not to be used as a [standalone] test,” she says. Some clinicians may also use a positive result prognostically, she adds, noting that one recent study shows faster disease progression in patients with the UIP pattern noted on Envisia testing.

“The important message is that the test is an aid,” she says. “The people who are using it see it as an additional piece of information.”

“It is a useful test,” she adds. “But it is not the magic test everyone wants.”

Talk to enough experts, and it soon becomes clear their concerns lie more with *mis*use of the test rather than its use. This is not an everyone’s-invited type of test; think minyan, not megachurch.

In Dr. Borczuk’s mind, “There’s no question that the Envisia can help. But it helps in the cases where the certainty is on the lower side, and the ability to get tissue is limited.” If the suspicion of UIP is high, Envisia should not be done, he says. When the question of treatment becomes somewhat binary, however, and an Envisia result can move the certainty from 50 percent to 80 to 85 percent, that can give physicians the confidence to provide a treatment that in the wrong patient could prove harmful.

If most pathologists don’t have extensive experience with these cases, the same is true for most pulmonologists. The Envisia test can be an appealing option for these clinicians, Dr. Borczuk says. “They simply know there’s a test that will give them an answer that will help guide therapy in a disease state that, frankly, doesn’t have a lot of great options.”

He compares the enthusiasm he’s seen for Envisia to that for liquid biopsy. Physicians may overlook what’s lost when a tissue biopsy is replaced by a liquid one, leading to inappropriate use. That’s where pathologist input pays off.

Dr. Borczuk advises colleagues to familiarize themselves with the literature and understand the cohort of patients in the clinical studies for Envisia, as well as outcomes and how test metrics were determined. Echoing others, Dr. Borczuk says, “Clinicians have a little bit of magical thinking about how this test works”—for example, that using any type of tissue will provide an answer. “I’m not saying the studies were not done well. But it’s a little naïve to think that the type of tissue completely doesn’t matter.” He takes it a step further and calls for future molecular tests of this type to include a preanalytic component that evaluates the tissue component. “The idea that you don’t need a preanalytic component for this test to determine whether you even have lung tissue in there is, I think, ludicrous.” While the implication is there, and his clinical colleagues have told him it doesn’t matter, “I’m not sure the data entirely supports that.”

Even if clinicians aren't asking about the test, that doesn't mean they're not already using it, as Dr. Borczuk learned. Pathologists can launch the conversation themselves. "It was worth it to me," Dr. Borczuk says. "I would have never known [what was happening] if I hadn't asked."

He did have a clue to start, he acknowledges. Might it be helpful to nose around even if you don't suspect a problem?

Dr. Borczuk reckons it's worth asking. "Because there is a possibility you're sacrificing both diagnoses—you're not getting the benefit of the Envisia test, and you're sacrificing the ability to obtain an alternative diagnosis. Pathologists who do have a relationship with the people who do bronchoscopy could reach out to say, 'Are you doing this test? How are you handling the distribution of the tissue to me?'"

That's not impolitic? "I think it's fine," Dr. Borczuk says. "Most pulmonologists recognize there's an interdisciplinary component here."

Across the country, Brandon Larsen, MD, PhD, at Mayo Clinic in Arizona, also reports seeing changes that he attributes to a growing use of Envisia.

"In our consultation practice, biopsy volumes have dramatically decreased," says Dr. Larsen, professor of laboratory medicine and pathology and consultant, Division of Anatomic Pathology.

Dr. Larsen was already familiar with the test, having been involved in its original validation.

He and his Mayo Clinic colleagues do not use Envisia, though he understands the appeal of the test from a clinical as well as a patient perspective. "It's a very attractive test," given that it avoids the risks of a lung biopsy in patients with compromised respiratory function. "When we decided whether or not this was any value to the clinical team and whether we should be doing this, originally our clinicians saw the potential advantages, but were not as familiar with the limitations and problems with the test."

Education filled in the gaps. "I think our clinicians benefited from pathologists who had intimate knowledge about the classifier—what it is, what it answers, what it doesn't answer, and what its limitations are," he says.

Dr. Larsen is concerned that merely identifying UIP does not provide an answer about the underlying etiology. And though the classifier isn't validated to discriminate among the various types of causes that can lead to UIP scarring in the lung, he says, "It's being used that way" in some practices.

Dr. Larsen

Dr. Larsen also notes that directing tissue to the Envisia test means other valuable information might disappear. "You lose a lot of nuance that's present in the biopsy." A pathologist might see a UIP pattern of fibrosis, but also, say, lymphoid hyperplasia suggestive of an autoimmune disorder, or granulomas that suggest hypersensitivity pneumonitis.

The transbronchial biopsy required by the classifier isn't a shoo-in, either. It's less risky than a wedge biopsy but doesn't eliminate risk. "What it does eliminate is a pathology assessment from the process."

Moreover, he has questions about what the classifier's impact is in the real world (Chaudhary S, et al. *Eur Respir J.*

2023;61[4]:2201245).

In his opinion—he makes it clear this is indeed his own personal opinion—the classifier is “an oversimplified and relatively crude approximation of reality, basically designed to detect advanced scarring. Which is nothing beyond what a good, high-resolution CT scan is able to detect.”

Not that anything in the field is simple, Dr. Larsen is quick to acknowledge. “Lung scarring is a difficult nut to crack,” he says.

“It can be frustrating for clinicians when they send a biopsy, and the pathologist comes back with a wishy-washy answer. I imagine that’s frustrating for patients as well.”

Dr. Myers

Dr. Myers, of Michigan Medicine, calls the field “a long-evolving discussion. People really struggle with diagnosing these conditions.” Over the years multidisciplinary discussion, with histology as just one of multiple ingredients, has essentially become the gold standard for diagnosis in diffuse parenchymal lung diseases, he says, codified in published clinical and diagnostic guidelines.

This comes with pluses and minuses, Dr. Myers observes, “but it has caused confusion about the role of histology” and can even lead to histology being undervalued at times in those discussions. (“Of course, as a pathologist, I’m biased,” he adds with a laugh.)

Dr. Groshong agrees this has long been treacherous terrain, with neither the radiology nor the biopsy being entirely diagnostic or specific. That has led to years of weekly interstitial lung disease conferences in which troublesome cases were diagnosed by consensus as much as anything. “A lot of these cases end up being kind of a preponderance of data,” he says.

From that perspective, he continues, “I think the Envisia classifier can tip the balance one way or the other, but isn’t the sole decider. We talk about it in the ILD conference along with all the other data,” including results from radiology and pathology. “But the reality is, the transbronchs almost never show UIP.” UIP tends to be a very peripheral predominant fibrotic process, near the pleura, he explains, while the transbronchial biopsy is done in the more central part of the lung. “So you’re almost biopsying the wrong region.”

One common scenario: a nonconfirming biopsy (“It doesn’t show the fibrosis, but everyone knows it’s there,” Dr. Groshong says), coupled with an imaging result that is nonclassic for UIP. For clinicians who are otherwise unable to find anything in the patient’s clinical history to sway them in a different direction, an Envisia classifier that reports UIP will be taken as weak evidence that the case is more likely UIP and IPF, says Dr. Groshong. “And if you don’t have a wedge biopsy, it’s better than nothing.”

Dr. Larsen, for his part, understands the appeal of the Envisia in practices that see very few interstitial lung disease biopsies. “I wouldn’t want to deal with it if I were out in community practice and saw something once a year. I wouldn’t feel confident whatsoever.” The appeal of simply putting a sample in a FedEx box and letting an expert figure it out is understandable, he says. “Problem solved, right?”

And based on what he’s seeing at Mayo—or, rather, not seeing, given the aforementioned drop in biopsies—that’s exactly what’s happening.

That's fine if clinicians are using it in the clinical context for which it is designed. "But it may or may not be providing the information they *think* it's providing them." That, Dr. Larsen says, is an argument for pathologists to understand their enduring role in educating others about testing. "A pathologist doesn't need to understand fibrotic lung disease to understand the limitations of an assay," he says, or to understand what a biopsy can reveal that a test like that classifier can't.

Given the fuzziness in the field, pathologists will likely face continued questions from colleagues who are Envisia-curious.

Though Dr. Groshong purposely didn't delve into those conversations at National Jewish Health, he's well acquainted with the ongoing questions colleagues have about the test. One regular question: How does it work?

"They want to know what genes they're looking at," he says. The question is nearly impossible to answer. This is a black box algorithm, he says, not a hand-created algorithm looking at individual gene transcription.

For clinicians, Dr. Groshong says, "That can be a hurdle—they're not always comfortable trusting something that's not explainable: *What genes are they looking at? Why is this working?"*

He's less bothered by the black box approach, citing his experience in using programming, machine learning, and AI to work with images. "I'm comfortable with this notion that things can work even though you can't necessarily interrogate network weights and figure out how they're working."

Others will need to become more comfortable with this shift in strategy, too, he suggests. "We're going to be seeing more of these tests, and not just in ILD, because machine learning is so good at making predictions off of data sets," including those that "you can't even imagine contain" the desired data. On large networks, by the time they're trained, it's no longer possible to look through the millions of network weights and figure out what corresponds to what, he says, or how it's being calculated.

Again, this doesn't particularly disturb Dr. Groshong. "In the end, all you can do is give it thousands of samples and show that its accuracy meets a certain expectation." That should have a familiar ring to it. "In reality, that's what we do in medicine all the time. That's how we validate lab tests. Even in pathology itself, our opinions are kind of subjective."

Some pulmonologists also ask whether the classifier can replace the wedge biopsy, Dr. Groshong reports.

"The answer is no. The wedge biopsy is always better if you can do it, but this is a good option if you can't for some reason." These questions are more likely to come from practitioners who have less experience with ILD and who think the classifier will "save" their patient from a biopsy.

"That's the wrong way to think about it," Dr. Groshong posits, since the biopsy will provide a better answer. The classifier is a second-line diagnostic tool, he suggests, if the patient is too old or frail to tolerate a wedge biopsy. "That's probably one of the most common misunderstandings in the community," he says. "A lot of pulmonologists like this idea that it's a fairly noninvasive way of getting an answer. But it doesn't give you the same quality answer as does the large biopsy."

"Some people view the test as a magic bullet and then want to use it on everything," Dr. Groshong adds. "That would be a mistake. I wouldn't not do a wedge biopsy on a patient just because I can do the Envisia instead."

Dr. Larsen too calls for pathologists to educate clinicians about the role of the test. Discovering a UIP pattern is, obviously, helpful. But he considers the lack of context to be the test's major Achilles' heel. "It's fine if clinicians understand that limitation, and they might still find it useful. But the devil is in the details, as always," says Dr. Larsen. "And clinicians look to us to provide that information."

When they don't, trouble ensues. Like Dr. Borczuk, Dr. Larsen compares the situation to liquid biopsies that bypass

pathologic assessment. “We know that pathologists aren’t perfect, and there’s always this desire to have the more perfect test that’s not biased by human opinion. We think that a result is going to be more precise if it’s generated from an instrument that eliminates the human from the process.” If only biology were that reductive, he sighs.

Lung scarring and lung fibrosis are complex, he continues. “You can’t reduce it to a binary result.” In other words, it’s not like a pocket Constitution a politician waves about as a simple explanation for how government works. “In the long run, it doesn’t do patients any favors” to avoid the heavy lifting of making a detailed diagnosis, Dr. Larsen says.

In his view, “We’re at a point where we can finally start understanding some of these problems at a deeper level, with the evolution in genomics and molecular testing. We can finally solve some of the mysteries that exist, that answer some of the remaining questions about these diseases in ways we never could have a couple decades ago.”

In that sense, Dr. Larsen continues, the step forward represented by a test like Envisia is terrible timing. “We’re our own worst enemies, because now we are eliminating humans from the process of evaluating these really complex disorders. We can make judgments that the genomic test can’t, and then put it into the larger context.”

Dr. Groshong identifies another bit of ironic timing. Two relatively new drugs, nintedanib and pirfenidone, can be used to treat progressive fibrotic diseases with a UIP pattern—knowing the underlying etiology may not be as critical as once thought, he says.

Indeed, he continues, before those drugs became available there may have been less pressure to make a diagnosis of UIP. “But now there’s this treatment dividing line: If it’s idiopathic UIP, then I’ve got two drugs; if it’s not UIP, I might be stuck.”

Dr. Myers agrees. When transplant was the only viable option, an accurate diagnosis mattered less. Even now, he says, the available drugs aren’t a cure, and they come with terrible side effects. “But at least it’s one of the first times this conversation felt important, because there are differences in what you can do for patients.”

And surgical biopsies have their own problems. Dr. Borczuk adds his own historical context, noting that as biopsies have been performed less often, and as tissue samples have become smaller—part of the ongoing story of trying to do more with less—some problems have become a self-fulfilling prophecy. “Not to say that we should biopsy patients simply to train pathologists, but this is one of the consequences of getting smaller tissue samples.” And when the cases are more challenging, “There are fewer and fewer people who have that experience to properly analyze it.”

Dr. Larsen identifies other problems with surgical lung biopsies. Once the tissue lands in the hands of the pathologist, he says, “One of the challenges we continue to grapple with in lung pathology is inconsistency and lack of criteria that would enable people to use a more confident, informed diagnosis.” Terminology is some 50 years old, he says, and despite some evolution, “We continue to use rather crude diagnoses for highly complex problems.”

Little wonder, he continues, that clinicians are eager for new tests, including those that, in practice, bypass pathology. A molecular classifier that appears to be an adequate surrogate is doubtless appealing. “It is a reflection of the struggles we continue to have in our field—to leverage these biopsies to be more clinically valuable, to learn more from them and provide more sophisticated diagnostic opinions.

“And we’re just not very good at that,” he says. Inter- and intraobserver variability is high even among experts, he says. “We don’t agree with ourselves on where those thresholds should lie, and we don’t have very good data from studies to refine the diagnostic criteria we use.”

There’s no shortage of opinions about Envisia, and it’s likely the tale will

continue to be told for some time, in many voices, medicine's version of a Viking saga.

"This is a glimpse of the future. Absolutely," says Dr. Myers. "As machine learning and artificial intelligence become more and more powerful, I think this is the first of multiple biomarkers to come that might eventually allow them to make these diagnoses without any sort of biopsy. This is going to become more common."

But, Dr. Myers continues, the real need is for better strategies on the therapeutic side, not the diagnostic side. As with many diseases, he says, "The issue is not so much precision as it is having an empty toolbox when it comes to knowing what to do about them."

Dr. Groshong predicts this is only the first attempt to produce a test in this area. "We haven't really had an ILD-specific lab test ever." Because Envisia has stepped somewhat successfully into this space, there will likely be others.

Because the two drugs are the first ever approved for IPF, he adds, and because they're so expensive, interest in the Envisia test was almost a fait accompli. Most payers would like to see a companion diagnostic for six-figure-type drugs, or at least some sort of diagnostic test that will suggest a patient is more likely to have the diagnosis in question.

He'd like to see more expansive classifiers, ones that could also identify, say, nonspecific interstitial pneumonia and hypersensitivity pneumonitis. A non-UIP diagnosis leaves physicians plenty of room for head-scratching, so "having classifiers that could flesh out that level would be helpful," he says, though he recognizes it would be hard to accrue enough patients for such studies.

"And then the ideal would be to get away from transbronch altogether," Dr. Groshong muses, eyeing the possibility of blood or sputum samples.

Dr. Lakticova holds out hope for a method that would allow genomic testing on material obtained by brushing the bronchial wall, for example. "Maybe we can progress eventually to a nasal swab. Maybe we are slowly transitioning from histology to genomics."

Dr. Borczuk would like pulmonology and radiology algorithms to more clearly incorporate when pathology is beneficial and to elucidate the expectations for particular biopsies. When biopsies are used in the wrong setting, "Of course clinicians get frustrated."

Dr. Larsen suggests the Envisia test represents a shortcut in a field that doesn't need one, though he completely understands the appeal of a quick fix, a sexy, binary test that everyone wants to use. "We all learn the hard way. And then our enthusiasm is tempered."

Long term, he'd like to see not only improved diagnostic criteria but also companion diagnostic markers. "The field is desperate for some kind of meaningful biomarkers that can predict response to therapy," including steroids and antifibrotic therapy. "We make a number of assumptions, but we don't have data yet." In his view, tissue-based tools will be key.

How hopeful is he this will happen? Dr. Larsen reports that on the pulmonary pathologist society level, there's been growing interest in developing consensus criteria, which in turn could be used as a basis for better studies. At the very least, he says, "We have to try to move in the right direction." Lung fibrosis pathology can learn much from advances in other fields, he adds, including neoplasia classification and workup.

He is open to the idea that the Envisia test—even as it irks him—might represent a step toward thinking differently about these long-standing problems. "Everyone agrees we need better tools, and I think the Envisia classifier is an inevitable result of our molecular revolution and a consequence of a lack of progress in pulmonary pathology for many decades." He adds: "Maybe it's useful in the sense that it's making us think of different ways of arriving at meaningful information." If there is indeed genomic information that can point to underlying disease processes or

likely response to therapy, “That would be hugely transformative,” Dr. Larsen says.

Karen Titus is CAP TODAY *contributing editor and co-managing editor.*