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A Phenotype-Driven Approach to Alpha-1 Antitrypsin Deficiency Care

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Grifols. Here's your host, Dr. McDonough.

Dr. McDonough:
This is *Clinician's Roundtable* on ReachMD, and I'm Dr. Brian McDonough. Here with me today to talk about the importance of moving beyond binary testing in alpha-1 antitrypsin deficiency—and how a more phenotype-informed approach can shape management decisions—is Dr. MeiLan King Han. She's a Professor of Medicine and Chief of the Division of Pulmonary and Critical Care at the University of Michigan Health. Dr. Han, welcome to the program.

Dr. Han:
Well, thank you for having me.

Dr. McDonough:
Let's dive right in, Dr. Han. Based on your experience, why do you think there's still such a strong reliance on serum AAT levels alone when evaluating for alpha-1 antitrypsin deficiency, and what are the risks of that approach?

Dr. Han:
So serum alpha-1 antitrypsin levels remain attractive to many clinicians because it's simple, inexpensive, and widely available. When you go to that dropdown menu in your electronic medical record, it's often the first thing that pops up.

But I think one of the challenges is that clinicians tend to think about levels in binary terms—either normal or abnormal—when in fact, alpha-1 antitrypsin deficiency is a lot more nuanced than that. And the serum level alone really doesn't capture the genetic risk or disease stability. So one of the challenges is that the protein is actually an acute phase reactant, and the levels can go up during inflammation or infection. And so you could have a patient with a high-risk genotype that truly is susceptible to developing disease, and they may on a given day—let's say they have a cold or some other infection—have what looks like a "normal" level.

The other challenge is that even within any genotype, we can see a broad range of values, such that sometimes even for a more severe genotype, you might see a borderline level.

And then I think a final challenge, particularly for patients who are carrying perhaps one normal allele and one more severe allele that puts them at higher risk like a PIMZ carrier, for instance, is that they may also show up as having borderline normal levels and may not always truly be detected.

So there are a lot of challenges with interpreting the alpha-1 antitrypsin serum level alone.

Dr. McDonough:
As a follow-up to that, can you walk us through why a normal AAT level doesn't always exclude alpha-1 antitrypsin deficiency?

Dr. Han:
Sure. So I think the first, as I mentioned, is that it is an acute phase reactant. It's made in the liver but can increase during inflammation, infection, or even pregnancy. So a single normal level shouldn't always lead someone to be completely reassured that they've ruled out significant alpha-1 antitrypsin deficiency.

As I mentioned earlier, the serum levels for various genotypes can actually overlap considerably. There's a range, and so again, this may give someone a false sense of assurance, particularly if the levels are borderline.

And finally, we also have to remember that there are a few rare dysfunctional variants where the level can look normal, but in reality, that's not functional protein.

So I think the bottom line is that if there's high suspicion, the level alone is likely inadequate.

Dr. McDonough:
So as we move beyond that single lab value, how should we start thinking about alpha-1 antitrypsin deficiency as a spectrum rather than a binary diagnosis?

Dr. Han:
So I think this is really an important paradigm shift for the field. For many years, we've thought about alpha-1 as being very black and white—either you have it or you don't; you're fine or you're not. But as I mentioned, the reality is a lot more nuanced than that. And even within a specific genotype, there's actually a continuum for risk.

So we know, for instance, the two normal alleles—MM—do confer normal levels of protection. We know that MS carriers—so they have one good and one impaired allele—can have lower levels than normal, but they generally don't develop disease. But then as we start getting into the more severe genotypes—MZ, SZ, and ZZ—we start seeing higher and higher risk.

But even then, the phenotypic expression in any one patient is going to differ just based on other factors, like disease biology and exposures. I have had patients who are ZZ that don't have significant lung disease, and then I have other patients who are SZ that had other exposures that were relevant and have severe lung disease.

So I think that the bottom line for clinicians is not just does the patient have alpha-1, but where does the patient fall on the spectrum? What's the genotype, and what are the other risk factors at play that contribute to the spectrum of severity that we see in any one individual patient?

Dr. McDonough:
For those just tuning in, this is *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. MeiLan King Han about moving to a genotype-driven understanding of alpha-1 antitrypsin deficiency and what that means for interpreting test results in practice.

Now, let's focus on ambiguity as a common clinical challenge. When the clinical picture and test results don't quite line up, Dr. Han, what factors signal that further evaluation is warranted?

Dr. Han:
Well, I think probably the biggest signal is if you see a discordance between the patient and the disease that you have in front of you and the lab result. So for instance, if you see someone with COPD, unexplained emphysema, or strong family history of liver disease and their serum alpha-1 antitrypsin level looks normal or maybe only even mildly reduced, that should cause you to pause and should raise some concern.

I think another area where I would pause and think I need to get more information is when you have borderline alpha-1 antitrypsin levels. This can be a clue that more information is needed. We mentioned that there can be all sorts of things that contribute to variation. If you have a patient that's reading out as mild deficiency but they have unexpectedly severe lung disease, that's another patient where I would think additional investigation with confirmatory genotyping is really important, and I'd do broader assessments for both lung and liver disease.

Dr. McDonough:
And once you work through that uncertainty, how does that clarity influence your management decisions?

Dr. Han:
Well, I think the management implications for an individual patient can be quite substantial. So if you have a patient with severe deficiency and a high-risk genotype, then establishing that diagnosis can lead to consideration for augmentation therapy, aggressive smoking cessation, and other lung preservation strategies, which over the long term can have huge impacts for individual patients.

For others who have an intermediate genotype, maybe instead of augmentation therapy, the focus will be on risk reduction and close monitoring, making sure the patients are avoiding inhaling anything that could be toxic, occupational exposures, vaccinations, and close surveillance for progression.

So management decisions should not solely be related to genotype. It's really about putting the genotype risk factors and the clinical picture all together.

Dr. McDonough:
Lastly, Dr. Han, since alpha-1 antitrypsin deficiency is one of the few genetic conditions where diagnosis has broader family implications, how do you approach cascade testing and counseling in your practice?

Dr. Han:
Right, so this is incredibly important. Once you've identified a patient with an abnormal allele, one of the important considerations then becomes, how do we communicate this to the rest of the family?

So I try to frame this as empowering for the patients as opposed to alarming. Just because a family member has an abnormal allele doesn't necessarily mean that they're going to have disease. Particularly for some of the intermediate risk genotypes, it's really about counseling and making sure that these patients have the opportunity to mitigate risk in their environments to help them preserve as much lung function over time.

So again, it's a really important point that once you identify a patient and you're treating the patient and you come up with a management strategy for that patient, the secondary onus on the physician is to say, "Okay, now we have to talk about the rest of your family. Let's talk about getting them tested as well."

Dr. McDonough:
With those real-world strategies in mind, I want to thank my guest, Dr. MeiLan King Han, for joining me to share practical approaches to interpreting complex test results and using them to guide management decisions in alpha-1 antitrypsin deficiency. Dr. Han, it was great having you on the program.

Dr. Han:
Thank you so much.

Announcer:
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