Cystic Fibrosis Carrier Screening: Tests in Age of Expanding Panels

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Cystic Fibrosis Carrier Screening: Tests in Age of Expanding Panels

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Narrator:
You are listening to ReachMD. Welcome to this medical industry feature entitled: ***Cystic Fibrosis Carrier Screening: Tests in Age of Expanding Panels****, sponsored by Quest Diagnostics. The following program is intended for US Healthcare Professionals only. Your host is Dr. Matt Birnholz.*

Dr. Birnholz:
Offering cystic fibrosis carrier screening to couples currently planning a pregnancy and to couples seeking prenatal testing has been a standard of care recommended by organizations such as ACOG and ACMG and the NIH for about two decades. However, recent advances in genome sequencing have expanded our understanding of the genetic basis of cystic fibrosis and enabled us to screen more patients for more CF-causing variants than ever before.

This is ReachMD. I'm Dr. Matt Birnholz. Today's program will be conducted in two distinct parts. First, to provide an academic view on the research-based updates in carrier screening for cystic fibrosis, I'll be speaking with Dr. Garry Cutting, Aetna/U.S. Healthcare Professor of Medical Genetics and Professor of Pediatrics at Johns Hopkins University School of Medicine. Dr. Cutting will share his perspectives on CF carrier screening, which are not on behalf of Quest Diagnostics.

Later in the program, I'll be speaking with Dr. Douglas S. Rabin, Medical Director of Women's Health and Medical Affairs with Quest Diagnostics to provide the viewpoints from a commercial laboratory.

So, Dr. Cutting, welcome to ReachMD.

Dr. Cutting:
Thank you for having me.

Dr. Birnholz:
Good to have you. So, let me start very basically, but it's sort of the million-dollar question, and that is: Why should we offer carrier screening for cystic fibrosis to all women?

Dr. Cutting:
If you consider the frequency of CF being approximately 1 in 2,000 to 1 in 4,000 in the general population and consider it's a severe, life-limiting disorder and it's one in which we now know the cause of this disease and we have some treatments for this disorder as well that have been successful, then making couples aware of their risk of having a child with CF seems quite prudent, and we have the tools to screen them efficiently.

Dr. Birnholz:
Now, over the years we have seen that the number of mutations in CF carrier screening tests offered in clinical practice have increased from the 23 that ACOG and ACMG recommended to now hundreds in some cases, so the first question is: Why is this? And then, what should practitioners consider when selecting a test for their patients?

> "Recent advances in genome sequencing have expanded our understanding of the genetic basis of cystic fibrosis and enabled us to screen more patients for more CF-causing variants than ever before."

Dr. Cutting:
Well, this is a bit of the mousetrap game. More is not always better, and it's something that one would think that if I have a panel that has a larger number of variants, then perhaps it would be more sensitive or more specific, but unfortunately, the problem is that we have a certain number of relatively common variants, and once we move away from the common variants, each of these variants become rarer and rarer to the point that they become truly rare in the population such that very, very few people carry them. So a test that has a very large panel of variants may not have that much greater sensitivity than a panel that is much more restricted, but because it has additional variants that are highly rare in the population, you start pushing against the accuracy of the test itself, of the method, because, in fact, you can have laboratory-based errors as frequently as rare people in the population carrying that same variant. So, there is a tradeoff between the number of variants you want to have and the sensitivity of that assay, particularly in a carrier screening modality. I'm not talking about individuals who have a phenotype that looks like CF. We're talking about healthy potential parents. And there's no way for us if you find a variant to know for sure it does or doesn't cause disease if you use a huge panel of variants, particularly if a lot of the variants have not yet been assessed for their disease liability.

Dr. Birnholz:
Well, let me then scale back and ask you another basic question with perhaps a complex answer, so I apologize up front, but why include certain variants and exclude others in CF carrier screening?

Dr. Cutting:
Carrier screening is a tradeoff. The issue is to provide a high-quality test with good sensitivity and specificity and to do it at a reasonable price so it has the greatest utility for the largest number of individuals. Putting together a test that has every single variant that's highly expensive, difficult to interpret, is not a useful carrier test. It is maybe useful in a diagnostic situation, particularly in challenging diagnostic situations, but for carrier screening, we've learned from Tay-Sachs, thalassemia in Sardinia and other places that you really need a discrete test, well-described variants, that works really, really well for the greatest majority of individuals and is cost-effective. So, that's why you don't put everything in there. You do the best you can for what you understand is the number of variants you want and, again, the... Also, you must consider -- I'll come back to this point -- as you start adding variants and you start adding the 200th, 300th, 400th variant, and then there's only a few people worldwide that carry those variants, when do you think a lab is going to see that variant ever? Probably never in certain cases. So you're screening for variants that a single lab, even a large lab, is unlikely to ever see. And so, what's the chance that you might have an error with the actual test itself? Actually, when you calculate it out, it's higher. The test can actually have an error that's false positive, and then you take a lot of effort to try to troubleshoot that false positive. So, you want to, again, run that test so that you minimize false positives. You work with true positives and you keep that test cost-effective and as sensitive as possible.

Dr. Birnholz:
So, Dr. Cutting, you alluded to false positives. Obviously, this is a major risk on one side of it, but why don't we turn to the other side, which is looking at the variants that are not known to cause classic CF? What issues arise there?

Dr. Cutting:
We don't know what to do with them. We're indeterminant, or variants of uncertain significance we call them, and some of them are of varying clinical consequences, because I think, as you alluded to, we know that variants in this same gene can contribute to diseases that are not cystic fibrosis but they cause male infertility, for example, or they can contribute in a complex way, to a multigenic way, to other diseases such as diffuse bronchiectasis or form a lung disease -- quite rare, but clearly CFTR has been implicated in that, we need to distinguish those variants from those that contribute to CF, and so when we say disease-causing, I really should be more careful. I should say cystic fibrosis-causing variants because you could argue there are ones that are male infertility-causing variants. There are ones that don't cause any disease as far as we know, but might, but we're not sure. And there are some that, in certain circumstances, cause male infertility, in other circumstances in a different person seem to cause mild CF, so those are very challenging to interpret, so we tend to in a screen modality really think of from the parents' perspective when we talk to them, they say, "Well, what I'm most concerned about is having a 1 in 4 risk of having a child with a life-limiting disorder," and that's cystic fibrosis.

> "If you consider the frequency of CF being approximately 1 in 2,000 to 1 in 4,000 in the general population and consider it's a severe, life-limiting disorder..."

Dr. Birnholz:
What about the question of variants in CF that relate to different ethnic populations?

Dr. Cutting:
Yes, it's a very important question, and it's one in which I know ACOG and ACMGG -- it was ACMG in those days -- struggled over. We know that this disorder is more common in the white European-derived population, but it's also been found in all populations and in every continent as well, and there's just rarer variants in those individuals. And the issue is, if I screen by the panel that was very specific for one population or another, would I have a better test? And I think to some extent for certain discrete populations that's still true, but in general, we're now moving much further afield in the amount of variants and the breadth of the variants that we collected, particularly geographically, and we're moving now towards near complete ascertainment of the variants worldwide. And this is what the CFTR2 project is doing, is collecting all these variants from nearly 90,000 patients worldwide, which is almost the entire population of CF patients. There may be a few that we're still missing in places like China and India, but we basically got near complete ascertainment, so we know all the variants that are out there. And when we now say, "Well, these are the most frequent ones," we're not including just the ones found in Northern Europe or in Southern Europe. We're talking about ones that are found in the Middle East or we're talking about ones that are found in areas of South America or in Hispanic individuals in the United States, because that's been another issue. So, we're including all these people now in these assays, in this collection of variants, and that information is now being interpreted into the design of the assays. So, yes, it's still an important issue with certain very discrete populations, but in general, it really is now a pan-ethnic racial agnostic test that one could offer.

Dr. Birnholz:
Dr. Cutting, we're covered an enormous amount of information in a very short amount of time. I congratulate you for that. But I do want to give you the chance to offer any other information, any other details that we haven't covered that you think would be of value and interest to our audience.

Dr. Cutting:
Well, just some thoughts about sequencing and, particularly, with the advent of next-generation sequencing, which has been a wonderful development where this is a case where sometimes more is really not better,

particularly when you're doing a carrier screening panel as opposed to a diagnostic test. So, if you're doing a diagnostic test, then a sequencing test that looks for everything is a great idea, but if you're doing a carrier panel where you've got, say, mom with a known mutation, dad uncertain, you analyze all of the coding regions of the gene by sequencing and you find things not in the carrier panel, not in any of the databases, then you're left with a very difficult situation for the couple. And in fact, there's a lot of variants that occur in this gene, 2,000 at least, and a big chunk of them don't actually cause disease, we believe, but we don't for sure know which ones do and don't, so the lab is left with a very difficult situation of saying, "I don't know if it causes disease or not," and now the couple has a difficult decision to make, particularly if a pregnancy is already ensued.

Dr. Birnholz:
With that I very much want to thank my guest Dr. Cutting for joining us on ReachMD today. Dr. Cutting, thanks again for your time.

Dr. Cutting:
Thanks, enjoyed being here.

Dr. Birnholz:
If you are just tuning in, this is ReachMD, and I am your host, Dr. Matt Birnholz. I just had the pleasure of speaking with our guest Dr. Garry Cutting about updates in carrier screening for cystic fibrosis.

Shifting gears, next up on our program I'd like to introduce Dr. Douglas S. Rabin, Medical Director of Women's Health and Medical Affairs with Quest Diagnostics. Dr. Rabin, great to have you with us.

Dr. Rabin:
Thank you so much.

Dr. Birnholz:
So, Dr. Rabin, to get us started, talk to us about the CF carrier screens that Quest Diagnostics offers.

Dr. Rabin:
We offer two screens. One is called CFvantage, 161 variants that we believe covers the most important variants that have been defined in the literature by Dr. Garry Cutting and his colleagues, and then we offer the 32 Mutation Panel which is reflective of the recommendations of ACOG and ACMG.

Dr. Birnholz:
And, Dr. Rabin, how did you decide on which variants to include in the CF carrier screens?

Dr. Rabin:
As I mentioned, we looked at the paper that Dr. Cutting and colleagues presented. And we determined that 161 variants could be demonstrated at a 0.01% incidence in the population and to cause cystic fibrosis according to three basic standards. 1)They determined the ability to cause CF either by demonstrating a clinical case where parents had a child that was affected or children or parents or adults that were identified had mutations; 2) they were able to look at those mutations and cell culture medium in a way to demonstrate that the transmembrane conductance receptor was affected, and in 3) they were able to demonstrate that the ability of the information to be converted into protein production was hampered in something called a stop codon. By looking at those techniques, they were able to identify the 161 most common mutations, variants, that will cause CF if they're present.

Now, what's important about this is that these variants also reflect pretty much all ethnic subgroups.

Dr. Birnholz:
Well, Dr. Rabin, what about any other areas that you'd like to touch upon for our audience that might be interested in, which you haven't had a chance to talk about, regarding Quest Diagnostics' role in CF carrier screening?

"Quest Diagnostics wants to highlight knowing. We want to know whether the choices in variants that we've made will give patients information that allows action from insight.

Dr. Rabin:
Quest Diagnostics wants to highlight knowing. We want to know whether the choices in variants that we've made will give patients information that allows action from insight. What that means is that those variants have to cause disease. And so, as I mentioned previously, they cause disease, because we've gone through a process looking at Dr. Cutting and his colleagues' papers and the methodology they used to choose our variants. We also know, based on that same work, that there are many, many variants that do not cause disease. We don't want to burden patients with the inability to know whether or not they're at risk. In addition, it allowed patients to have some assurance that they weren't getting more than they should, they weren't getting less than they should.

We really think that this screening assay covers all the areas that are important. It's pan-ethnic, and, finally, it gives information that can be justified completely in the literature. We really believe that it's the best thing for patients that we can offer.

Dr. Birnholz:
With that, Dr. Rabin, thanks so much for your time today.

Dr. Rabin:
Thank you very much. It's been my pleasure.

Narrator:
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