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Healthcare Solutions

CONTRACTOR ADVISORY COMMITTEE MEETING SUMMARY

Topic: Molecular Diagnostic testing to identify Acute rejection in Kidney or Liver Transplant Recipients
Date: November 16, 2022

Co-Facilitators:

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Subject matter expert's potential conflicts of interest are displayed in Appendix A

Background

The purpose of this Contractor Advisory Committee (CAC) meeting was to discuss evidence on molecular diagnostic testing to identify acute rejection in kidney or liver transplant recipients. The role of a CAC Subject Matter Expert (SME) is advisory in nature, and comments and/or opinions on the evidence or literature are intended to assist the Contractor Medical Directors (CMDs) in determining if a proposed LCD should be developed or if an existing LCD should be revised. A set of selected publications was shared with the SMEs prior to the meeting however, additional publications may be used to inform any policies that may result from the proceedings. CAC SMEs' comments and/or opinions supplements the Medicare Administrative Contractor's (MAC's) internal expertise and ensures an unbiased and contemporary consideration of "state of the art" technology and science. This meeting summary includes the topics of discussion and the SMEs comments/opinions on those topics. It also includes results from the poll questions.

Topics of Discussion

During the CAC meeting, SMEs were asked to provide comments and/or opinions on the evidence as it relates to the use of AlloMap, AlloSure, Prospera, Viracor TRAC, QSant, kSORT, TruGraf, and OmniGraf in kidney or liver transplant recipients. More specifically, is there sufficient evidence on the:

- patient population in which the test is to be used
- clinical context (i.e., testing for-cause vs. Surveillance) for use of the test
- test's precision (i.e., performance indices reported with or without confidence intervals)
- test's clinical utility (i.e., the frequency and timing of testing)
- test's threshold/cutoff, what may influence these, and whether these have been standardized
- test's ability to discriminate acute T-cell mediated rejection and antibody-mediated rejection from quiescence

- clinical scenarios when testing would preclude the need for biopsy
- predictive value of test results and whether it would guide clinical management when a biopsy is not performed
- overall level of confidence that the test can accurately indicate rejection or quiescence
- test's use is necessary for specified patient-centered outcomes

Based on the topics, questions were developed to facilitate a robust discussion as well as to be used for SME polling. Summary results from the discussions and polling for kidney transplant recipients are outlined below. In addition, the SMEs agreed that there is a paucity of evidence for molecular diagnostic tests used in liver transplant recipients; therefore, no detailed discussions or polling related to the use of these tests in liver transplant recipients were conducted.

Kidney Transplant Recipients

Test(s):, AlloSure, Prospera, Viracor TRAC, QSant, kSORT, TruGraf, OmniGraf

1) Is there sufficient evidence to identify the patient population that the molecular diagnostic could be used? (e.g., risk level, ethnic/cultural demographics, repeat transplant recipients, etc.)
   a) *Summary of Comments/Opinions*

The tests appear to have some utility in all patient populations, and there is still emerging evidence for patients undergoing repeat transplantation, and across demographics (3)

I'm not aware of any ethnic culture, demographic differences. I am aware of some age differences. If that matters, I mean, kids matter a little bit. But it's older people that are a little bit different because they might have a falsely elevated donor-derived cell-free DNA because most of them are, it's relative, it's the percent of the donor-derived cell-free DNA divided by the recipient's cell-free DNA and if this recipient is small and elderly that might artificially raise the percentage

Retreat, repeat transplant recipients, that's been pretty well looked at. It's a little bit more elevated when you have 2 or 3. But, it's, it's usable. And that gets on to, I think you're going to have a later question, oh there it is, multi-organ? What about multi-organ?

Well, with multi-organ. I think where it might be useful is establishing a baseline for that individual after the initial transplant when the cell-free DNA would be, have gone down to a baseline. Usually, by two weeks or so. That's where I think it'd be useful and it's looking like simultaneous kidney-pancreas' their baseline might be a little bit more than then what a kidney is, as opposed to a lung transplant, it looks like they've got about the same 1% cutoff.(5)

I didn't want to hog the show. But, so, the gene expression panel, the AlloMap, for example, is a kidney set, now focused gene expression panel, that came out of the hearts.

The hearts was really good, it was, it was helpful to try and discriminate rejection from not, or quiescence from non-rejection, it looks like that paperwork, but I haven't seen it being used

clinically with that. The TruGraf or OmniGraf gene expression panel, is, again, out of Northwestern, Dan Salomon's kind of work. You have to be a little bit suspect about the centers that develop the data that were used. And John Friedewald makes a big deal about borderline rejection. I think, I think he's leading the transplant lemmings off the borderline rejection cliff, because I think that, I don't know, there's a reason it's called borderline.

And so, I'm just worried about over interpreting that. I think we can not talk about QSant and kSORT, I don't think they're going to, they're seeing the light of day. So, I learned, I wouldn't waste a lot of time with them. I understand that the company QSant has gone under and that was Minnie Sarwal's and she'd been part of kSORT and, I, believe, many people have tried to replicate kSORT data and have not been successful. So, I think we can not spend much time talking about them, and I'll let others talk now.(30)

Yes, this is Steve, I think Dan put it much more bluntly and boldly than most would have. But I think he's completely accurate in his description of some of the entrance here and then in this space, in broad strokes. It's pretty clear that the cell-free DNA is just further along, the development pathway, it has more robust data. Um, and, as we think other folks have pointed out, I think, AlloSure, the data is the most robust, but these are all promising.

So, I think we'll, just, kind of, earlier in the process for some of the multi-modality testing and knowing where they're going fit in the market and how useful they are going to be. It's also concerning that some of them, we haven't really seen that those data that they are promising, are generalizable to the whole population of the country.(32)

b) *Poll Results: Discussion only, no poll was conducted for this question*

2) Is there sufficient evidence on the clinical context (i.e., for-cause vs. surveillance) in which the molecular diagnostic test could be used?

a) *Summary of Comments/Opinions*

I think that there is probably pretty good evidence for TruGraf and OmniGraf in surveillance and cell-free DNA probably can be used in both contexts.(2)

Surveillance verse for-cause. Um, we don't have a lot of data there. From the Dart study, there were some programs that did surveillance biopsies and I think that might help to sort out, because I see there's that many programs 18% of kidney programs do a surveillance biopsy. I would advocate against doing any surveillance biopsy because we already know it's bad data. So now you get bad data that makes you get cell-free DNA, or maybe not. Or you start treating someone based on histology, which we know isn't very good. So, I have a problem with that. Proximity to pulse. I'm not sure that that matters.(5)

Well, with regard to whether that means that we should, or we shouldn't, use these biomarkers for surveillance, I think that's a different question. That still, at least the long-term data, in terms of whether or not if you use one of these surveillance tests and you find a rejection and you treat it, does that make an impact on long term survival? That has not been worked out.(9)

From, the evidence that, we have seen so far. Obviously, you know, with time we'll see if this translates to improve survival or, you know, improve long-term survival, I mean, you know, we, we're sort of being judged on one-year survival, know, what about, you know, maybe 10-year survival in these patients. Maybe we'll capture a few more rejections or a few more graft dysfunctions down the line with surveillance. So yes, the data is still emerging for that, but I think in the immediate experience that most of us have, it shows that you can avoid, um, certain risks to patients, by using some of these tests.(12)

So, you know, I think that this technology really hasn't seen its full use yet. Yes, of course, we have to show evidence that, that, you know, it can detect rejection and whatnot. But I think that really, the future is going to be monitoring surveillance, not just for-cause, but surveillance of stable patients.(14)

b) *Poll Results:*

	Response			
Test	Evidence clearly indicates for-cause use only	Evidence clearly indicates surveillance use only	Evidence clearly indicates for-cause and surveillance use	Evidence does not clearly indicate a clinical context
AlloSure	1	0	5	0
Prospera	1	0	4	1
Viracor TRAC	3	1	0	2
QSant	0	0	3	3
kSORT	0	0	1	4
TruGraf	2	2	1	1
OmniGraf	0	1	0	1

3) In the existing evidence, what is the level of confidence (or certainty) regarding test performance data reported without any confidence intervals?

a) *Summary of Comments/Opinions*

I don't think you assign valid confidence intervals to gene expression panels, right? I mean, it's reads, I don't think they have a confidence interval.(20) ..... it's just a different, it's a different type of data. I don't think it's amenable to confidence intervals. I may be wrong, but I don't think you do.(22)

With respect to the question about confidence intervals, I do think they're important, right? That's just a standard way of statistical reporting, However, if you have multiple studies showing, the same thing, then your confidence, even in the absence of confidence interval, does increase but yeah, in general, I think confidence intervals are important.(26)

b) *Poll Results:*

	Response		
Test	High confidence	Low confidence	No effect
AlloSure	4	1	0
Prospera	4	2	0
Viracor TRAC	2	3	1
QSant	2	4	0
kSORT	0	5	1
TruGraf	1	4	0
OmniGraf	1	3	1

4) Is there sufficient evidence to support the utility of surveillance (i.e., not for-cause) testing in kidney transplant recipients?

a) Summary of Comments/Opinions

The tests appear to have some utility in all patient populations, and there is still emerging evidence for patients undergoing repeat transplantation, and across demographics (3)

I think that the cell free DNA tests have been there's sufficient evidence to show that they are pretty good in, both for-cause and for surveillance. Um, you know, that's my experience, and that's sort of some of the data that I've been able to review. So, at least from my standpoint, and from what I've read in the literature, there's sufficient evidence for its utility in for-cause and surveillance (3)

b) Poll Results:

	Response	
Test	Yes	No
AlloSure	5	1
Prospera	5	1
Viracor TRAC	1	5
QSant	1	5
kSORT	0	6
TruGraf	3	3
OmniGraf (TruGraf + Viracor TRAC)	3	3

4a. If yes, what is the appropriate testing schedule based on the published evidence?

i) Summary of Comments/Opinions

So, we should be doing this with some, regular frequency, whether that's, you know, at month 1, 2, and 3 and then quarterly or months you know monthly for the first four months, I mean I don't know. I think that we need more data, and we need more time to sort that out, and see what the practice patterns are, and understand the cost benefit, because, again, the societal cost is going to be very large, but if we get it right, then the societal benefits can be enormous. In terms of further out, I don't know. I think, I think that, you know, that we should be testing at some frequency, particularly with cell-free DNA. I don't know where gene expression profile is going to end up in that sort of spectrum of a normal surveillance of stable kidney patients.(35)

So, in my responses for surveillance, I basically said there's a lack of evidence for anything. But I think that that has to be nuanced a little bit. I think there's evidence for it being useful. The problem is, is it worth it? So, I think, for the AlloSure test, for example, that there was a, the admiral study, shows that it shows what the cell-free DNA went up, an average of about three months before there is a clinical event, associated with injury, whether that was rejection or something else. But the percentage of people that had had such an event, were, like, less than 10%. So that means 90% of people are undergoing multiple testing at significant cost, with generating false positives, that might cause you to react, and be associated with cost and convenience, and maybe harm. So, I think that, yes, it, there is evidence that it is, it could be used, but it hinges on the word utility, what, what is it, so is it useful? It depends on what you're looking to use it for.(36)

I mean, if you want to stick to the evidence, I mean, there is no direct evidence to say that a specific testing schedule should be endorsed. But, yes, I mean, I think it would probably, at this point, be center- specific, but in terms of being supported by evidence, there's no specific data there to tell you.(42)

Yeah, I mean, which, I think, is kind of, exactly right, and the points that I raised earlier is we really don't know and the problem that you have from a population standpoint is, the majority of transplant programs are using this promising technology. So, the, the cart is getting out a little bit in front of the horse. You're going to be seeing very widespread adoption without knowing, ultimately, what's the impact on long term allograft survival, which I think is, you know really the big issue that we need to address, but we do know this is better at doing certain things, than what there are sort of legacy platforms. And so, the best guess that I can come up with, that makes sense, is based on the limited extent data, like, for example, what was done in DART?

You know, what testing frequency should you use? The other thing to bear in mind, independence of population like it's true if it's a low-risk or a high-risk population, the important thing is we do know that these are important to obtain longitudinally and so we can see the change over time, in the, and again, I'm talking, I'm not talking about GEP, I'm talking about cell-free DNA. But we want to be able to see the relative change value over

time. That's very useful on our clinical decision making, so that would speak towards some regular frequency of surveillance, rather just one and done. (43)

So, I think it's going to have to be very, you know, it just ends up being very center-specific. By and large, because center's practices in terms of who gets transplanted are divergent. You know, not everyone does the same thing. Immunosuppression protocols aren't the same and surveillance protocols aren't the same.(46)

So, we've tied ours in when we would do DSA testing, but as I said, I'm beginning to think we should stop doing DSA testing and then, if we have an abnormal, donor-derived cell-free DNA, then we should get the DSA rather than what has been, historically been, the other way around. Because, as I said, 50% of the DSAs are not clinically meaningful. I don't know that we can say that 50% of donor-derived cell-free DNA, above 1% are not meaningful. I'm not, just not sure of that. So, the typical surveillance would be at one month, three months, six months, nine, and twelve. And whether you should do long-term, then that's also, a little bit similar to what we actually do 1 through 6 months testing for BK. Because we do have good data that BK comes up in the first three months. We want to get the stragglers when you don't need to start it before a month. So, we're trying to make it, at the same time that we do our donor-specific antibody or BK testing, but as Ali said, about, how often do people do protocol biopsies, surveillance biopsies, it's changed, but I would say it would have been early on people would get them really at 3 and 6 months and a year and that, I think most people see that that's too much. When we do studies, we do them usually at six months a year, and a year and maybe two years. (47)

Now, I also want to just touch on and hopefully we can elaborate on the timeframe that you all discussed regarding a testing schedule for the cell-free DNA test, and, you know, in some respects it seemed that it was it was hinged on the timeframe of protocol biopsy. So, if you could clarify that a little bit better, that would be helpful. Um, I know you did say some of those schedules are influenced by the timing of other testing? That's, like, BK virus testing and things like that, but, if you could elaborate a little bit further, that would be very helpful. And, at the end of the day, what we want to understand is, yes, how is this being used? But, but, you know, the evidence that supports that use is critical. The evidence from the literature.(48)

I think, at least for me, it's hard to answer, because I think we've already touched on that, that, I don't think, at least, if it's going to be supported by evidence, that there isn't that support. But I do think it's probably reasonable to, if you were going to use it, to use it at a time where you would be considering doing things like DSA or in other programs where they would be doing protocol biopsies. So, at least in my mind, something like at six months or 12 months, but that's not supported by data whatsoever.(49)

So, I mean, you're asking a difficult question because to me, what's the data if ask us, what's the data for the frequencies for which you should obtain a serum creatinine? It's, it's more about global practice patterns than it is about data to support it, right? It's all based on guidelines, but

how do we really know? And, so, if you look at the literature, we, I think the paper by Bu and the paper by Gupta both useful in showing us that we can identify rejection that we are otherwise would have missed, and so there, you know, and that's a useful piece of information, because those are, for the most part rejections, that are valuable to treat, that benefit patients. But ultimately, we don't know what frequency we should be obtaining surveillance molecular testing and it's to be determined.(50)

5) Is there sufficient evidence on the ability of the molecular diagnostic test (or combination of tests) to discriminate **acute T-cell-mediated rejection** from quiescence?

a) *Summary of Comments/Opinions*

The tests are generally non-specific, and they couldn't be used alone to be able to distinguish between T-cell mediated rejection and quiescence or antibody-mediated rejection in quiescence. There is some data that would indicate at least for cell-free DNA if you use it in conjunction with the DSA, it's more likely to be antibody rejection, but even in that case, you still can't rule out that there's a mixed rejection there. So, in the end of the day, you probably going to still need, you're definitely going to still need, to do a biopsy in order to know what rejection you're dealing with. (52)

.... because if you get an elevated test and you're not going to know whether that's quiescence, TCMR or ABMR, so you can't, you just can't know. You can use the test result to tell you this is antibody rejection, or this is T-cell mediated rejection, at least when they used alone.(54)

Yes, you can distinguish quiescence if, if it's low risk, if the likelihood of rejection is generally pretty low, anyway, and you get a reassuring test that, in that context, negative predictive value is high, it's very likely to be quiescent. But on the flip side, if you have a high-risk patient, creatinine is going up, drug levels are low and you get a negative test or a low-level cell-free DNA, for example, you probably should still biopsy them because the likelihood of a false negative is going to be higher. So, it does depend on which context you're in to determine your level of confidence of quiescence.(65)

I've been amazed at how the cell-free DNA doesn't go down for a long time in either T-cell mediated or antibody mediated rejection, if at all, and it begs to question of really, how often do we really reverse this thing and, what, what is the measure for it?(70)

b) *Poll Results:*

	Response	
Test	Yes	No
AlloSure	4	2
Prospera	5	1
Viracor TRAC	2	2

QSant	0	6
kSORT	0	6
TruGraf	2	4
OmniGraf (TruGraf + Viracor TRAC)	3	2

6) Is there sufficient evidence on the ability of the molecular diagnostic test (or combination of tests) to discriminate **antibody-mediated rejection** from quiescence?

a) Summary of Comments/Opinions

The tests are generally non-specific, and they couldn't be used alone to be able to distinguish between T-cell mediated rejection and quiescence or antibody-mediated rejection in quiescence. There is some data that would indicate at least for cell-free DNA if you use it in conjunction with the DSA, it's more likely to be antibody rejection, but even in that case, you still can't rule out that there's a mixed rejection there. So, in the end of the day, you probably going to still need, you're definitely going to still need, to do a biopsy in order to know what rejection you're dealing with. (52)

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b) Poll Results:

	Response	
Test	Yes	No
AlloSure	3	3
Prospera	3	2
Viracor TRAC	2	3
QSant	1	5
kSORT	1	5
TruGraf	2	4
OmniGraf (TruGraf + Viracor TRAC)	3	3

7) Are currently published thresholds/cutoffs affected by the time post kidney transplant?

a) Summary of Comments/Opinions

Time post-transplant is important. There is an elevation from ischemia reperfusion that goes away.(5)

Think one thing that hasn't been said, I agree with what everyone else has said so far is that the timing and sort of the timeline of when a cell-free DNA essay is abnormal versus a transcriptional assay is abnormal, they are very different. So, they're really measuring different timeframes. The half-life of this of the changes in the signal are different. And so, you know, I think some of that may have to do with the behavior of the approach.(33)

If the cell-free DNA is below the threshold, I feel pretty confident that the patient, if the patient has low cell-free, cell-free DNA, and they have an elevated creatinine, that becomes a judgement call. One will need to look at the clinical picture to determine whether a biopsy is indicated or not. So, those are those are those are my thoughts on that.(85)

b) *Poll Results:*

	Response	
Test	Yes	No
AlloSure	4	2
Prospera	4	2
Viracor TRAC	3	2
QSant	2	3
kSORT	1	4
TruGraf	2	2

7b.Based on the evidence, for kidney transplant recipients, what should the appropriate thresholds/cutoffs be for the tests below?

i) *Summary of Comments/Opinions*

I think where it might be useful is establishing a baseline for that individual after the initial transplant when the cell-free DNA would be, have gone down to a baseline. Usually, by two weeks or so. That's where I think it'd be useful and it's looking like simultaneous kidney-pancreas' their baseline might be a little bit more than then what a kidney is, as opposed to a lung transplant, it looks like they've got about the same 1% cutoff.(5)

Just where I think the gene expression panel said, that's a little strange, that question doesn't really work the donor-derived cell-free DNA, I mean, people on the panel have written about that and now it's changing. So, one was a powerful number. I think it still is, but .7 a good number, .5 is a good number. So, I think, I think, we're just learning more.(75)

i) *Poll Results: Discussion only, no poll was conducted for this question*

8) Is there sufficient evidence to indicate that in patients **without signs and symptoms** of rejection, use of the molecular diagnostic test (or combination of tests) would preclude the need for kidney biopsy?

a) Summary of Comments/Opinions

Oh, I mean, it depends on what you mean by signs and symptoms of rejection, but if you have like, we've had patients with persistently elevated DSA, who, without the ability of having cell-free DNA, we would, we would repeatedly biopsy those patients, where we are now comfortable enough to avoid additional biopsies. So, that's, that's a reasonable, I think, statement with limited, sort of, it's an anecdotal statement, but it's a reasonable one.(78)

I agree with that statement.(79)

So, with, the test definitely helps us avoid biopsies in the scenarios that you've mentioned. One, a patient comes in with an elevated cell-free DNA and their creatinine is elevated or they have symptoms, whatever those may be, that patient will get a biopsy in my center. Let's say that the patient has an elevated cell-free DNA and their creatinine is normal. I feel pretty confident in biopsying those patients as well. Because I feel like, you know, based on evidence, that, you know, there may be something going on with a kidney. Whether it's, you know, may be rejection, and may be BK, something is awry.

If the cell-free DNA is below the threshold, I feel pretty confident that the patient, if the patient has low cell-free, cell-free DNA, and they have an elevated creatinine, that becomes a judgement call. One will need to look at the clinical picture to determine whether a biopsy is indicated or not. So, those are those are those are my thoughts on that.(85)

For me, philosophically, if you're going to send a test, then you should act on those results. So, for example, if you send an AlloSure and it's high, and you decide not to biopsy, it begs the question of, why did you send it in the first place? So, I think, philosophically you should use the test.

The question is: who are you using it in? And then also that does depend on the patient mix, and it depends on which test you're talking about. For example, in the surveillance question where primarily I guess what you're asking is, can it replace a protocol biopsy? It depends on what kind of rejection, you're, you think that patient might have, and it also depends on which tests you're going to use. So, for example, I know that there's been a lot of talk about how TruGraf, the gene expression, can help us to avoid protocol biopsies and subclinical rejection. But most of these, that, that test was mostly validated on TCMR, I mean, most of the cases in those in that validation study where TCMR and much less so for antibody rejection and they have shown that that test is not as sensitive for picking up antibody rejection.

So, if you have somebody who has a positive crossmatch and you estimate that they're probably going to have about a 35% risk of antibody rejection, and you use TruGraf to decide not to biopsy them, that might not be the right decision. But if you're, on the other hand, if you're looking at a low-risk population that, you know, that, it's probably not at risk for antibody rejection, doesn't have DSAs, it's unsensitized and the rejection you're planning on seeing are probably going to be TCMR. Maybe TruGraf is a good test, right? Or at least as a better test. But then you would be arguing, well, if they're that low risk anyway, why are you doing the protocol biopsy in the first place?

So, there's a lot involved in thinking about how to answer this question. But, you know, the answer really is, it depends, right? It depends on a lot of things.(86)

b) Poll Results:

Test	Response Yes	No
AlloSure	6	0
Prospera	4	1
Viracor TRAC	3	1
QSant	3	2
kSORT	1	4
TruGraf	4	1
OmniGraf (TruGraf + Viracor TRAC)	4	1

9) Is there sufficient evidence to indicate that in patients **with signs and symptoms** of rejection, use of the molecular diagnostic test (or combination of tests) would preclude the need for kidney biopsy?

a) Summary of Comments/Opinions – see Summary of Comments/Options from question 8.

b) Poll Results:

Test	Response Yes	No
AlloSure	5	1
Prospera	3	2
Viracor TRAC	2	2
QSant	1	4
kSORT	0	6
TruGraf	3	2
OmniGraf (TruGraf + Viracor TRAC)	3	1

10) Is there sufficient evidence on the ability of the molecular diagnostic test (or combination of tests) to guide clinical management without kidney biopsy?

a) Summary of Comments/Opinions

I want to provide a slightly different perspective that is in agreement with pretty much what everyone says. But, 25 years ago, people thought, you know, putting a camera on a cell phone is ridiculous, and completely unnecessary, because not only are the, the images not good enough, but also, everyone has digital camera and you know, whatever. I think this technology here provides us the opportunity for repeated measurements of very specific allograft injury.

And I think we've largely focused, so far, on detecting rejection, and treating rejection, maybe early. But what we haven't really focused on is not seeing rejection when we're trying to alter immunosuppression. And I think that you know, we shouldn't forget that the drugs we give these patients, for immunosuppression themselves are never toxic. And in trying to save them from rejecting, we're actually injuring their kidney chronically.

So, having a tool that allows you to safely go down on immunosuppression and be, you know, relatively certain without biopsying it, all the time, that you are at a safe level of immunosuppression, allows you to actually prolong graft function and graft durability.

So, you know, I think that this technology really hasn't seen its full use yet. Yes, of course, we have to show evidence that, that, you know, it can detect rejection and whatnot. But I think that really, the future is going to be monitoring surveillance, not just for-cause, but surveillance of stable patients.(14)

So, with, the test definitely helps us avoid biopsies in the scenarios that you've mentioned. One, a patient comes in with an elevated cell-free DNA and their creatinine is elevated or they have symptoms, whatever those may be, that patient will get a biopsy in my center. Let's say that the patient has an elevated cell-free DNA and their creatinine is normal. I feel pretty confident in biopsying those patients as well. Because I feel like, you know, based on evidence, that, you know, there may be something going on with a kidney. Whether it's, you know, may be rejection, and may be BK, something is awry.

If the cell-free DNA is below the threshold, I feel pretty confident that the patient, if the patient has low cell-free, cell-free DNA, and they have an elevated creatinine, that becomes a judgement call. One will need to look at the clinical picture to determine whether a biopsy is indicated or not. So, those are those are those are my thoughts on that.(85)

For me, philosophically, if you're going to send a test, then you should act on those results. So, for example, if you send an AlloSure and it's high, and you decide not to biopsy, it begs the question of, why did you send it in the first place? So, I think, philosophically you should use the test.

The question is: who are you using it in? And then also that does depend on the patient mix, and it depends on which test you're talking about. For example, in the surveillance question where primarily I guess what you're asking is, can it replace a protocol biopsy? It depends on what kind of rejection, you're, you think that patient might have, and it also depends on which tests you're going to use. So, for example, I know that there's been a lot of talk about how TruGraf, the gene expression, can help us to avoid protocol biopsies and subclinical rejection. But most of these, that, that test was mostly validated on TCMR, I mean, most of the cases in those in that validation study where TCMR and much less so for antibody rejection and they have shown that that test is not as sensitive for picking up antibody rejection.

So, if you have somebody who has a positive crossmatch and you estimate that they're probably going to have about a 35% risk of antibody rejection, and you use TruGraf to decide not to biopsy them, that might not be the right decision. But if you're, on the other hand, if you're looking at a low-risk population that, you know, that, it's probably not at risk for antibody rejection, doesn't have DSAs, it's unsensitized and the rejection you're planning on seeing are probably going to be TCMR. Maybe TruGraf is a good test, right? Or at least as a better test. But then you would be arguing, well, if they're that low risk anyway, why are you doing the protocol biopsy in the first place?

So, there's a lot involved in thinking about how to answer this question. But, you know, the answer really is, it depends, right? It depends on a lot of things.(86)

b) Poll Results:

Test	Response Yes	No
AlloSure	0	0
Prospera	0	0
Viracor TRAC	0	0
QSant	0	0
kSORT	0	0
TruGraf	0	0
OmniGraf (TruGraf + Viracor TRAC)	0	0

11) Would you perform a kidney biopsy if the molecular diagnostic test indicates rejection, but the patient exhibits no signs and symptoms of rejection?

a) Summary of Comments/Opinions

b) Poll Results:

Test	Response Yes	No
AlloSure	0	0
Prospera	0	0
Viracor TRAC	0	0
QSant	0	0
kSORT	0	0
TruGraf	0	0
OmniGraf (TruGraf + Viracor TRAC)	0	0

12) How confident are you in the evidence that, for this test, an elevation in donor-derived cell-free DNA indicates **T cell-mediated rejection**?

a) Poll Results:

	Response				
Test	Not at all confident	Slightly confident	Somewhat confident	Fairly confident	Completely confident
AlloSure	0	2	2	1	0
Prospera	0	3	1	1	0
Viracor TRAC	0	3	1	0	0
QSant	2	2	0	0	0

13) How confident are you in the evidence that, for this test, an elevation in donor-derived cell-free DNA indicates **antibody-mediated rejection**?

a) Poll Results:

	Response				
Test	Not at all confident	Slightly confident	Somewhat confident	Fairly confident	Completely confident
AlloSure	1	1	0	2	0
Prospera	0	2	1	1	0
Viracor TRAC	0	2	1	1	0
QSant	2	2	0	0	0

14) How confident are you in the evidence that, for this test, the test results can accurately indicate rejection?

b) Summary of Comments/Opinions

c) Poll Results:

	Response				
Test	Not at all confident	Slightly confident	Somewhat confident	Fairly confident	Completely confident
kSORT	3	1	0	0	0
TruGraf	0	1	1	0	0