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Regulation of Microbiome-Based Diagnostic Tests:

Aim 2 - Provider Focus Group Findings

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1. Background

The overall goal of the *Regulation of Microbiome-Based Diagnostic Tests* project is to inform and support policy and regulatory approaches that will encourage innovation and scientific discovery of new microbiome-based products, while identifying and addressing regulatory concerns from researcher, physician, and consumer/patient perspectives. There are 3 Aims for this project:

- *Aim 1* – Review the federal and state laws and regulations that govern diagnostic testing and results to determine if they are appropriate for microbiome-based diagnostic tests.
- *Aim 2* – Understand stakeholder perceptions of microbiome-based diagnostic tests including test utility and value to health care decision-making and concerns with regard to privacy and data security. Conduct in-depth interviews and focus groups with three groups of stakeholders – microbiome researchers, providers, and consumers/patients.
- *Aim 3* – Develop and propose an appropriate and comprehensive regulatory framework for microbiome-based diagnostic tests. A multidisciplinary working group will review findings from Aims 1 and 2 to assess the current regulatory position for microbiome-based diagnostics and evaluate the appropriateness and effectiveness of that position.

The anticipated goal of this project is to develop a comprehensive review of the current legal and regulatory landscape, assessment of stakeholder perceptions of microbiome-based diagnostics and understanding of legal protections to inform an evaluation of the existing regulatory scheme and identification of a feasible, patient-centered approach to the regulation of microbiome-based diagnostics.

1.1 Purpose of Report

This report presents findings from Aim 2 focus groups conducted with providers. Findings from Aim 2 interviews with microbiome researcher, physicians, and focus groups with patients/consumers can be found in corresponding reports. Findings across all stakeholders for Aim 2 will:

- Identify the characteristics, motivations and perceptions of patients currently engaged with microbiome-based diagnostic tests;
- Determine under what circumstances potential consumers would or would not order such tests;
- Identify the education, demographic characteristics, practice variables and perceptions of providers ordering these tests for their patients or concerns they have about ordering such tests;
- Determine how well patients and providers understand the test results; and
- Elucidate potential legal or social implications of these diagnostics that should inform their regulation (e.g., potential for use by health insurance companies).

2. Methods

2.1 Participant Recruitment and Characteristics

Provider participants were recruited from the following: 1) providers who have ordered diagnostic tests from uBiome on behalf of their patients; or 2) professional associations such as the American Gastroenterological Association and/or the American College of Obstetrics and Gynecologists. Outreach to providers were conducted in collaboration with the University of Maryland Medical Center, UMB and the UMB PATIENTS Program. All recruitment materials were approved by the Institutional Review Board of the University of Maryland, Baltimore.

Table 1 describes participant characteristics by physician type, as well as the number of focus groups and participants.

Table 1. Characteristics of Focus Group Participants (N=19)

Physician Type	Number of Focus Groups	Number of Participants	Percentage of Total Participants
Gastroenterologist	2	6	31.6
Pediatric Gastroenterologist	2	5	26.3
OB-GYN	2	5	26.3
Functional Medicine	1	3	15.8
TOTAL	7	19	

2.2 Focus Group Data Collection

Focus group discussions were led by one of three trained facilitators who are members of the research team. A co-facilitator who also was a member of the research team was present during all groups to take notes and manage the logistics. All participants provided consent before the start of the session. Out of concern for attendees' health and safety during the COVID-19 pandemic, the workshop was conducted virtually using Zoom. Participants were asked to join the focus group from a computer or laptop, and use their device's video camera so all participants could see one another, similar to an in-person gathering. The discussion was recorded with permission of all focus group participants. Focus groups lasted approximately one hour.

Focus group moderator guides were developed based on the data collected in the individual interviews. Separate guides were developed for physician focus groups and patient/consumer focus groups. All guides included semi-structured questions that were used by the focus group moderator to facilitate the discussion. The physician focus group guide is located in Appendix A. Broad topics for the focus group guide included:

- Knowledge of and experience with available microbiome-based diagnostic tests;

- Motivation to order microbiome-based diagnostics tests;
- Perceptions of the risks and benefits of microbiome-based diagnostic;
- Attitudes toward alternative/complementary medicine;
- Understanding of mock test results for a gut microbiome-based test and a vaginal microbiome-based test (for OB-GYN focus groups);
- Interpretation of the clinical validity, reliability, and utility of microbiome-based diagnostics to clinicians and consumers; and
- Perceptions of the regulation of microbiome-based diagnostic tests.

2.3 Data Sources

Multiple data sources were analyzed for relevant information, as described in Table 2 below.

Table 2. Focus Group Data Sources

Source	Description	How used in analysis
Transcripts	Transcriptions based on focus group recordings	• Transcripts were imported into NVivo® 11 • Text was coded per the codebook (See Appendix B)
Summary notes	Notes taken by the co-facilitator during the interviews/focus groups	Notes provided additional context and insights to coded text
Focus group videos	Video recordings of the focus groups	Notes provided additional context and insights to coded text

2.4 Analytical Considerations

2.4.1 Data Management

The focus group Zoom recordings were professionally transcribed verbatim. A member of the research team reviewed the transcripts for accuracy and completeness. All transcripts were anonymous and any names of individuals, facilities, or other item that could compromise confidentiality were removed from the transcripts. Once validated, the facilitator posted the transcripts on a secured drive where members of the research team could access the data for analysis. Using standardized procedures, transcripts were formatted and imported into NVivo® 11 for analysis.

2.4.2 Data Analysis

Broad content areas and potential themes of interest based on discussions with the research team were explored. The initial broad content areas identified were:

- Experience with consumer tests

- Perceptions of microbiome tests
- Motivations for testing
- Attitude towards integrative medicine
- Understanding sample results
- Regulatory issues

The initial identification of content areas and themes was meant to be as expansive and inclusive as possible so that the analysis would capture the breadth and depth of issues discussed. In this manner, additional content areas and themes emerged during data analysis. Throughout the process, the research team discussed prevalent concepts and themes that were mentioned in numerous focus groups. The research team developed a codebook (Appendix B) to document these concepts and themes. Throughout the coding process, the codebook was refined as codes were merged, expanded, deleted or divided. Previously coded text was recoded to reconcile variability.

The qualitative analyst utilized NVivo® 11 to code and analyze the transcripts. Passages of text relevant to the initial content areas were selected and codes were developed that reflected emergent themes. To provide in-depth perspectives of specific themes and to identify trends, coding reports were created to cross-reference coded text with physician type.

2.4.3 Coding Rules and Meetings

Prior to the start of analysis, the research team met to discuss and agree on the organization and use of the codebook. The research team met regularly to discuss the status of coding, analysis, interpretations, and modifications to the codebook. Additionally, the research team discussed the provider focus group analysis in relation to the Aim 2 researcher and provider interviews to assess any congruence or differences in the coding, analytic process or findings between the samples.

3. Results

The following sections detail the themes and subthemes that emerged from the focus group discussions. Descriptions of themes, as well as quotes are included; attributions to participant type are in parentheses after each quote.

3.1 Experience with Microbiome-Based Diagnostic Tests

All providers were asked about their experience with microbiome-based diagnostic tests, as well as if they have ordered these tests for patients. Almost all physicians across focus groups were aware of microbiome-based diagnostic tests, either through their practice, research, or from patients requesting interpretations of their results. The use and ordering of these tests, however, varied by physician groups.

3.1.1 Provider Experience with Ordering Microbiome Tests

More than other groups, functional medicine physicians had the most experience with these tests, some reporting that they ordered these tests for 5% of their patients, while others ordered these tests for the majority of their patients. One functional medicine physician stated that she has worked with a company that produces microbiome-based diagnostic tests and has a fair amount of experience reviewing results. In terms of ordering these diagnostic tests, functional medicine physicians stated that this was one among a larger panel of tests used to gain a larger understanding of the patient's gut and overall health. Physicians stated that these diagnostic tests were not used in isolation, but in conjunction with other standard tests.

> It's a part of complete workout that we'll do with patients, since we know the importance of microbiome and gut health and overall health in terms of autoimmune diseases and other chronic diseases. It's part of that to make sure that we get what's going on. If you're looking in the gut microbiome test for obviously, severe dysbiosis, but also other markers of digestive efficiency and inflammation, we'll [do] the stool test. *(Functional Medicine Physician*)

> Let me just say that when we order the testing, in our practice, we order it as part of a broader array of sequel parameters, stool parameters. We get the microbiome, but we get some other pieces as well and so, when you ask why do you order the testing, we order it because we want to see a full picture, not just any way because we're trying to look at the actual microbiome results. *(Functional Medicine Physician*)

Another functional medicine physician explained that he also used microbiome-based diagnostic tests as an educational tool for patients, "*I also use it as an educational tool for patients, in helping them to understand the relationship between the diversity of their microbiome and the diversity of the foods that they're eating.*"

Adult gastroenterologists and pediatric gastroenterologists were familiar with these tests as well, particularly if they were involved in fecal transplant research, but stated that they did not order them for patients. As one participant stated, "*I did the fecal transplants in affiliation with Mass General and we've always used capsules, but I do not have experience with this test.*"

Of all physician groups, OB-GYNs were less likely to be familiar with these diagnostic tests and did not report ordering them for patients.

3.1.2 Provider Experience with Patients/Parents Ordering Microbiome Tests

Several reported that some of their patients have either taken the test as ordered by a functional medicine physician, or through a direct-to-consumer (DTC) company, and have asked assistance with interpreting test results.

> I'd seen a few patients with direct-to-consumer type arrangement. I think what I see more often is perhaps a homoeopathic or naturopathic provider who's ordered the test through their practice. I think I see that more than direct consumer. But I've seen both. *(Pediatric Gastroenterologist)*

Several pediatric gastroenterologists stated that it was patients with various GI symptoms with no physical causes that that often take DTC tests, seeking answers to their complex health issues. Physicians also explained that parents of children that have not shown improvement through conventional treatments, or are on the autism spectrum, have ordered these tests and asked assistance to interpret findings.

> It often is families that have had challenges in finding what they see as therapeutic relationships or diagnostic answers to their questions. I think in addition to patients with irritable bowel, we see patients who have functional syndromes. So, functional abdominal pain, and also a number who have children who are on the autism spectrum. They'll often come in. Rates of GI diseases and GI symptoms in particular are higher in our autism population. And so, often these families really struggle with having children who have significant behavioral needs. And then on top of it to add GI symptoms that range from belly pain to aggression to constipation to diarrhea. They'll often come in with these tests looking for answers. *(Pediatric Gastroenterologist)*

Table 3. Summary of Experience with Microbiome-Based Diagnostic Tests

Experience with Microbiome-Based Diagnostic Tests	GI	Ped GI	Ob-Gyn	Functional Med
Provider Experience with Ordering Microbiome Tests *Experience with ordering tests for patients*				X
Provider Experience with Patients/Parents Ordering Microbiome Tests *Experience with interpreting results for patients/parents*	X	X		X

3.2 General Perceptions of Microbiome-Based Diagnostic Tests

Providers were asked about their perceptions of whether microbiome-based diagnostic tests were primarily considered an advancement of modern medicine or alternative/complementary medicine, as well as potential harms of these tests.

3.2.1 Modern Medicine vs Integrative Medicine

When asked if physicians believed that microbiome-based diagnostic tests were considered an advancement of modern or integrative medicine, the vast majority of providers believed these tests to be a form of integrative medicine. Functional medicine physicians stated that providers in their field are often early adopters of new tools and methods to improve clinical practice.

> What I find is that within functional medicine, we're early adopters and we're focused on clinical translation of bringing new tools into the marketplace, whether we're talking about in blood samples of HSCRP or homocysteine or other kinds of markers of inflammation or in stool, where we're talking about inflammatory markers, like calprotectin and pancreatic elastase, which are not commonly used by GI doctors around the world. Those were brought forth by functional medicine physicians to be able to demonstrate the utility of them. They were first to market there. I do believe that there will be aspects of this that will become common practice in the future. I don't know whether it'll take five or 15 years for that to happen and there will be a further development. *(Functional Medicine Physician*)

> I think that functional medicine in general are early adopters, we tend to be in that translational space of really understanding or trying to understand what's in the science literature and using that information to guide clinical practice. There have been many times, what is it 20 years ago, we were talking about microbiome and leaky gut before microbiome was even discussed or even accepted in the medical world. Now, in the medical world, people or everybody is talking about the microbiome. At least there's an understanding across the world of its importance in overall health. *(Functional Medicine Physician*)

Although traditional providers did not view microbiome-based diagnostic tests as a part of their practice, several did emphasize that these tests do have the potential to be clinically useful, once the field has developed a greater understanding of the microbiome. Currently, these tests were not viewed as applicable to their practice, as it is unclear how to interpret findings in a meaningful way to improve patient health. This is also presented in Section 3.4 Perceived Clinical Utility of Microbiome Tests.

> I agree that I think this will become or can become part of mainstream medicine and that's where our research is heading and we're learning more and more about the microbiome, but this current test with the information we have now, I don't think is appropriate for current practice, that I'm aware of. *(Gastroenterologist)*

Several pediatric gastroenterologists stated that these diagnostic tests represented neither modern nor integrative medicine, but rather, “an advancement in technology and potentially science. But it doesn't really advance either traditional or complementary medicine. As neither side of that knows particularly how to interpret those results and how to make them actionable.”

3.2.2 Perceived Harms of Microbiome-Based Diagnostic Tests

Providers across all groups were concerned about potential harms that microbiome-based diagnostic for consumers.

Following microbiome test recommendations may lead to worse health outcomes. In particular, all providers were concerned that these tests may present recommendations to address a specific microorganism, which may not have clinical relevance. Additionally, addressing specific microorganisms through the use of therapeutics or dietary elimination diets may be harmful and disrupt the complex, symbiotic nature of the microbiome, leading to worse health outcomes. Providers expressed that this was of particular concern for the DTC tests, where patients may implement these interventions without consulting a physician. In addition to potentially affecting health outcomes, focusing on specific microorganisms may delay the detection and treatment of the root cause of the health issue.

> A lot of these tests are done in a direct-to-consumer model, versus through a physician. I think that when a physician orders, we have the luxury of also getting a lot of information about that patient. We know their history, we know what's going on, we have all of the other bloodwork, the metabolites, etc., that we use to put the results of the microbiome test into context and then that's where it becomes valuable to us as treatment. When it's used all by itself as the only thing that's being done, I think that that can be very misleading for people and could potentially cause... Depending on how it's interpreted and recommended, that could potentially cause harm. *(Functional Medicine Physician)*

> Again, I think that it also has to do not only with that, but also with the way in which the reports are written where there's too often I would say, in over interpretation on the meaning of the amount of a specific species. It has to be looked at in context of how the community is working together and what it's producing. You see some of these reports, where basically it's saying, "Oh, you should have more of this and so, do this treatment to get more of this specific species," or "Do this treatment to get rid of these species." We really don't have data to support that. From a systems standpoint, it doesn't even make sense to do it that way and then we see reports that come out that say. *(Functional Medicine Physician)*

> By going down this treatment pathway, you're delaying addressing the underlying problem and restoring your health and for some illnesses, that's not, that delay is not insignificant. You know, a long delay in Crohn's disease can result in the development of complications, which are not amenable to medical therapy and require surgery. *(Gastroenterologist)*

Physicians in the gastroenterology and pediatric gastroenterology groups were also concerned about the effect of restricting foods based on the list of recommended foods to eat and those to avoid in the microbiome diagnostic test recommendations. Pediatric gastroenterologists were worried that patients may restrict their diet too severely due to these tests, leading to greater health issues. In particular, they were concerned for pediatric patients who need enough calories and nutrition for proper growth and development. One pediatric gastroenterologist noted that she has seen patients develop avoidant Restrictive Food Intake Disorder (ARFID) after following microbiome or food intolerance testing recommendations to avoid certain foods.

> One of the things that may help is if you referenced, you have a genotype, that means you should eat X, Y and Z or you're predisposed to oxalate formation or whatever, you should put a

reference there that they could click and says, "Okay, here's the science that says this genotype of Micro-biome equals high oxalate formation," something like that. *(Gastroenterologist)*

But what I usually see them eliminating are things like, fresh fruits or dairy or things that have had calcium content and things like that. No one's going to die from eliminating bell peppers. But usually, it's things that either the kids love to eat, or the things that have high nutritional value. If you get a kid on a restrictive diet, then they can really be missing a category of food or missing certain nutrients or missing calories. *(Pediatric Gastroenterologist)*

Providers may prescribe harmful or unnecessary treatments based on microbiome test results. Physicians also stated concerns of tests that were ordered by providers and not DTC, particularly if the provider was not well-versed in microbiome research. A few traditional providers also viewed these tests as an opportunity for holistic providers to order tests and sell baseless products to take advantage of their patients. The costs of these treatments, including probiotics, herbs, and dietary changes, were a concern for traditional providers.

Hopefully, practitioners have a better understanding of the context, but that's not always the case. You're absolutely right. There are many practitioners who want to see, they'll do a microbiome test so that they have something to do oftentimes, I see it is killing the bad guys, whatever that is. We know that certain, even parasites and things can be very normal constituents of a microbiome without causing harm and so, if you just see it or you see high levels of a certain so-called harmful organism, the first thing that a lot of practitioners want to do is go in there with some kind of anti-microbial, anti-parasitic, anti-fungal intervention that could have an effect of disrupting the rest of the microbiome and cause harm. I agree that there is potential even in practitioner's hands. *(Functional Medicine Physician)*

The problem is that right now a lot of those tests are being ordered to meet it's like a means to your end. So, if I want to prescribe some holistic treatment and unfortunately what I'm seeing is, we have a lot of "Naturopaths," who want to prescribe some herb that's going to fix everything for this patient. So, then they do a microbiome sequencing and saying, "Oh, look, your microbiome is such and I'm going to give you this pill or bottle that you're going to buy at $500 a month and you're going to take it and it's going to improve your microbiome," and that I think, again, is in the nonsense category and that's where I'm seeing it used now. *(Gastroenterologist)*

People are getting these treatments that are not inherently, completely benign. I think of any population is problematic, but it also can waste time because you're not grounded and thinking you have some bacteria when there may be something else that you're not allowing us to pursue, because you've been convinced that there's something in the group. *(Pediatric Gastroenterologist)*

Microbiome test results and recommendations may cause fear and anxiety for patients. Pediatric gastroenterologists and OB-GYNs, in particular, expressed concern over microbiome-based diagnostic tests, as the recommendations provided do not consider the patient's history or focus on specific microorganisms that are actually quite common and not clinically relevant, thus causing anxiety and fear for consumers. As many of these tests are DTC, the patient may subscribe to unnecessary or harmful protocols and interventions to address these fears.

As I said earlier, agree with using alternative methods as well as dietary approaches. I'm a huge fan of the role that diet can play in health and disease. Now, with the results as described here, first, you present us with a patient who's anxious, depressed and has gone through a lot of treatments but seem to have not been effective. So, to give an already anxious patient a test with results that are almost definitively saying, "You have intestinal barrier dysfunction. There's pro-inflammatory bacteria in your guts." these are things that one can say, "We are concerned that there might be." You can use language like that, but when you present to this anxious patient that, "I now have a problem with my gut, we've identified it. You're in the red zone, the bad zone." I don't know if that necessarily is the message you want to give this patient who's already set up. *(Pediatric Gastroenterologist)*

So I mean, just looking at this particular report, the ones that I would be concerned about they were positive would be the chlamydia, the gonorrhea and gent, the syphilis, those are things that I would want to explore further in terms of whether or not they're truly positive or negative. Almost everything else like cervicitis I'm like, "Yeah, lots of women have cervicitis"…I wouldn't be concerned about that at all, but the patient may be overly concerned about it because she doesn't know how common it is. *(OB-GYN)*

The cervical cancer is just something that's too inflammatory to cause people alarm, because there are lots of women that may have high risk HPV and if you have that positive under cervical cancer, oh my gosh, how do you talk her down off the ledge for that? So, I just think that's too inflammatory. And that will just cause a lot of unnecessary anxiety given how common it is. *(OB-GYN)*

Microbiome tests may affect trust between patient and provider. Pediatric gastroenterologists and OB-GYNs spoke about how these tests may erode the relationship between the patient/family and provider, particularly when the patient/family may place more trust in the recommendations than the provider. These physicians also explained that it is difficult to communicate with patients/families if these tests were ordered by a holistic provider, whom the traditional provider may not agree with. Physicians also spoke of the need to rebuild the trust and communicate with the patients/families to help them understand how to appropriately interpret the findings.

But I think when families have results in their hands, particularly if they have results with perhaps, like in the example you guys sent around with recommendations, again, those haven't come from me, but it is hard to break them of that opinion. So, they come to the visit with maybe a traditional provider, with their own opinions and agendas. And so, that's one of the other dangers, right? It's hard to change opinion. *(Pediatric Gastroenterologist)*

So, when there's "medical tests" that are available for patients and their families, but sometimes I think the families get this a little bit more distressed. Why did you not work this? Why did you not look into this more? Which I think demeans that relationship a little bit, too. That's the only other thing that I could see is a little bit of a problem. *(Pediatric Gastroenterologist)*

And now it's like if companies are directly going straight to the "consumer" as opposed to the patient, it's like they're going straight to them. But then it's like, the consumer will then come, they're our patient and we have to have this discussion. And it depends on how much trust your patient has with you whether or not they actually will trust your advice versus this company with this…because the report looks pretty neat and official. So, I kind of feel like they may be

> falsely assured by that, like, “Well, how is this allowed that this company can do this?” But then when I go talk to my physician physicians they’re like “no”. So, I'm not sure that they will take away that hope from that discussion, like, “Okay, Dr. [physician] said that she doesn't trust the results and whether or not they'll be happy with that.” They may be happy during that encounter. But who knows what they'll do when they go home? Because I could just say, for my patients, now, my patients use a lot of things from Amazon, somewhat on the web, all sorts of crazy herbs and mixes no matter what I say. But so, I think it may kind of erode that relationship. So, in terms of harm, yeah, that will be really concerning. *(OB-GYN)*

For pediatric gastroenterologists, this may occur when parents consider a variety of traditional and non-traditional treatments to address their child’s severe diagnosis.

> I've seen a handful, including one yesterday of patients who have very severe cancer diagnoses. Children with very aggressive cancers, the families are often looking for alternative and complementary. There, it's very hard to draw a line and say things aren't helpful when they're desperate. But it's often that these desperate families that are autism, cancer or things like that. *(Pediatric Gastroenterologists)*

Risks for inaccurate results for sexually transmitted infection tests. The OB-GYN groups were concerned about the accuracy of these tests, given the little information they received on how these tests detect STIs. These physicians also discussed the potential harms of patients receiving false-negative results for sexually transmitted infection tests, as well as the difficulties for the physician to interpret these findings to their patient. Additionally, false-negative tests for HPV was also a concern, as HPV positive patients may not seek attention from their medical provider.

> If somebody gets that syphilis result and it says negative, they're gonna feel falsely reassured that they definitely don't have syphilis? I think that's a big problem, because the way that we would diagnose syphilis of various sorts would be serology because, perhaps you'll catch it if they had a chancre in the vaginal area. But if they had latent syphilis or they had a primary shift list with a chancre in a very different area, anyway, a variety of scenarios that would not catch syphilis. So, the patient could be falsely reassured that they don't have the condition, when in fact, they do. So, I think those two things, potentially create a lot of problems, confusion and anxiety for the patient, and then difficulty with a doctor having to figure out how to sort through this result and deal with it. And then secondly, false reassurance for the patient where they think, “Oh, I'm great, even though perhaps there was that risk, I don't have to go for further test time.” *(OB-GYN)*

> What do you do with discordant results? If somebody had a high-risk HPV Pap within the last year, didn't follow up. And then, they do this direct-to-consumer tests that potentially has a false negative and then avoids care or something like that. That would be concerning scenario. *(OB-GYN)*

Table 4. Summary of General Perceptions of Microbiome-Based Diagnostic Tests

General Perceptions of Microbiome-Based Diagnostic Tests	GI	Ped GI	Ob-Gyn	Functional Med
Modern Medicine vs Integrative Medicine *Perception of tests as an advancement of integrative medicine*	X	X	X	X
Perceived Harms of Microbiome-Based Diagnostic Tests				
Following microbiome test recommendations may lead to worse health outcomes	X	X	X	X
Providers may prescribe harmful or unnecessary treatments based on microbiome test results	X	X	X	X
Microbiome test results and recommendations may cause fear and anxiety for patients		X	X	
Microbiome tests may affect trust between patient and provider		X	X	
Risks for inaccurate results for sexually transmitted infection tests			X	

3.3 Perceived Accuracy of Microbiome Tests

Physicians across all focus groups were asked how they would generally interpret microbiome tests' clinical validity and reliability to clinicians and consumers. Additionally, physicians were provided mock microbiome-based diagnostic test results, which included a case study of the consumer; results of various types of bacteria, yeast, fungi, and stool PH; ratings of the consumer's inflammatory activities, digestive efficiency, intestinal barrier health, pathways, metabolic fitness; and recommendations on when and what to eat to improve these ratings.

All physician groups stated that they had difficulty interpreting test results as they were unsure of the accuracy of these tests. For example, physicians expressed concern about the sample obtained, laboratory testing processes, and validity of results.

3.3.1 Appropriateness of Samples for Microbiome Tests

A few physicians in the gastroenterological and functional medicine group questioned the use of stool samples to accurately assess the microbiome. These physicians stated that although it is relatively feasible and non-invasive to test stool samples, particularly for DTC tests, this sampling method cannot accurately reflect the composition of the intestinal microbiome. Thus, these physicians questioned the validity and usefulness of these tests as there are significant differences in microbial composition between mucosa and feces.

> I have some concerns of even using stool for testing for some of these things. So, if you're looking at transcripts, as an example, you're looking at RNA, gene expression, RNA is extremely labile. It changes second to second and it degrades very, very quickly. What you're doing is you're not actually getting an assessment of the microbiome; which majority is in the colon.

You're getting an assessment of what's happening in the rectum and actually the ecosystem of the stool once it's out of the body because you're going to get changes as soon as it's exposed to air. I think that we have to step back and even look at what can we interpret from using stool as our testing source in terms of how much that really reflects the entire microbiome, when a lot of the literature is written on the importance of the mucosal microbiome. I think there's the bigger level, those are the questions you need to be asking, in terms of how helpful these are clinically. (*Functional Medicine Physician*)

I don't think we have any idea what you can actually measure versus what's on the mucosa that you can't measure, which is in the mucus layers. I just don't think we know enough. (*Gastroenterologist*)

I don't know that I can tell from what was presented, the conditions in, which the sample was collected, but there's no reason to expect that you wouldn't see overgrowth with everything that was cultured and reported out and that the conditions that it was collected are important and can certainly impact reliability. *(Gastroenterologist)*

I guess we're just talking about the results. But also, we're assuming that the tests have been collected appropriately. Is this something that patients would collect on their own? Or is this something that would be done in a setting of a visit? Does it matter when in their menstrual cycle, the test is being collected? *(OB-GYN)*

3.3.2 Perceived Analytical Validity of Microbiome Tests

A few physicians also raised questions about the analytical validity of microbiome tests. For these participants, they were concerned about the laboratory's assay's ability to detect variants in the microbiome, and whether this process was standardized across various DTC tests. Physicians also noted that while typical lab results referenced ranges for what is considered "average," the mock results did not provide this information. Additionally, this report did not state how ranges were determined and on which populations they were normed. This lack of clarity regarding ranges and algorithms contributed to the lack of trust in results. One pediatric gastroenterologist stated, "I worry about how these tests were performed." A gastroenterologist also stated:

I would suggest there be some kind of standardization in the process of doing these tests, so that you know if different labs are doing it they're using the same process and your results are comparable. (*Gastroenterologist*)

I think knowing how the covered samples were collected, what format, what platform do they use to actually do the testing. And if we want to be particularly nitty gritty, I mean, how deep was the sequencing? (*Ped Gastroenterologist*)

How was it cultured and then what is the reference population? To say something as high or to give a normal range, you have to know what it's compared against. It's really hard to determine what that is in any other way and then these ones are the algorithms of many different transcripts coming from the microbiome that, again, you would need to know the details of how it was determined, what were the actual transcripts that went into this score, what is it

compared against? There's a lot of unknowns that make this really hard to interpret. *(Functional Medicine Physician)*

3.3.3 Perceived Clinical Validity of Microbiome Tests

In terms of clinical validity, participants across all groups questioned the degree to which microbiome tests are able to accurately identify or predict a risk of disease or other outcomes. This perceived lack of clinical validity was often discussed in conjunction with concerns about the sampling method and analytic validity of tests.

A number of participants, particularly among the gastroenterological and pediatric gastroenterological groups, suggested that companies that manufacture these tests should provide data on how they determine clinical validity. The lack of these data made it difficult for physicians to have confidence in the validity of the results. As one pediatric gastroenterologist stated, "*I rarely find it to be useful because well, firstly, you don't get much information about how they perform the test to see how valid they are.*" A gastroenterologist explained the need to assess the predictive ability of these tests, "*they'd have to validate it, they'd have to do this in 1000 patients and see, if they can confirm that something was predictive*." Across all groups, physicians stated that they have not ordered microbiome tests for their patients as they were unsure of their validity. A gastroenterologist stated,

> If I ordered [it for] a patient, I want it to be scientifically valid. I don't want it to be some guy trying to sell some herb that, you know, "I'll sequence your microbiome and then I'll sell you an herb that's going to fix everything. (*Gastroenterologist*)

Table 5. Summary of Perceived Accuracy of Microbiome Tests Theme

Perceived Accuracy of Microbiome Tests	GI	Ped GI	Ob-Gyn	Functional Med
Appropriateness of Samples for Microbiome Tests *Concerns regarding the use of stool samples for microbiome tests*	X			X
Perceived Analytical Validity of Microbiome Tests *Concerns about perceived analytical validity, including laboratory processes used*	X	X	X	X
Perceived Clinical Validity of Microbiome Tests *Concerns of perceived clinical validity, including predictive ability of test results*	X	X	X	X

3.4 Perceived Clinical Utility of Microbiome Tests

Participants in all physician groups were asked about their thoughts on microbiome tests' clinical utility, including the degree to which results can be used to determine treatment decisions or improves the

management of patients. Physicians across all groups stated that while they do believe that there is potential for microbiome tests to be used for diagnostic and treatment use and are interested in a "clinically actionable" outcome for these tests, there are several challenges to their clinical utility at this time. Participants provided several reasons for this, including the lack of analytical and clinical validity, limited understanding of the microbiome, and need for additional testing and evaluation to determine how to best utilize test results. Providers in the functional medicine group, however, stated that they do use microbiome tests in conjunction with other assessments, but do not solely rely on these results to make treatment decisions.

3.4.1 Limited Understanding of the Microbiome

Several participants across physician groups stated that our current understanding of the microbiome has not advanced to the point of understanding the complex criteria for a healthy microbiome, what is needed to prevent dysbiosis, and the relationship between specific bacteria and health conditions. Often, microbiome test results will focus on the presence of a few, specific bacteria. With the current understanding of the microbiome, it is difficult to comprehend the impact of these bacteria in the context of the larger microbiome environment. Participants explained that due to this limited understanding, it is not possible to use microbiome test results to guide treatment options. Some participants, also explained that even if physicians were confident in the analytical and clinical validity of the tests, they would not be able to draw any clinical conclusions from the tests due to this limitation. As several participants stated:

> Sometimes it's not just the bacteria that are there, but what they're doing. And that bacteria live in communities like people, and so, taking things out in isolation may not work, which is why probiotics, which I'm a big fan of in theory, often don't end up proving as useful because giving back a single or even a few bacteria that are helpful is probably not enough for more serious conditions. I do tell them that I think that that's the future, and that they should continue to ask questions and explore. (*Ped Gastroenterologist*)

> Again, once I think we understand better which species we really need to build up for what particular characteristics we're hoping to achieve in the patient or how do you tweak the microbiome to achieve immunity, what is the criteria for a healthy microbiome to prevents C. diff., colitis, to alter obesity, etcetera. I think it absolutely will be the way of the future. It just isn't there now. (*Gastroenterologist*)

> I could perhaps understand the desire to look for a bacteria that can cause bacterial infections, but this is just not, close to what we would do for clinical practice and so, yeah, so I guess I'm still grappling with how to describe it in a way that I would feel comfortable saying out loud, but I guess I would say that they were able to grow some bacteria and fungi and complete a pH test and apparently get some data on the presence of a variety of genes that predict certain metabolic functions. But I think beyond that, it's a leap to say that that's predictive of any genotype for this particular patient. *(Gastroenterologist)*

> I think they're very valuable, but looking at very specifics in terms of what type of probiotic, I think that there's still a lot we need to understand about the microbiome to get really good at that kind of interpretation. *(Functional Medicine Physician)*

> Just because the microbiome test picks up on five different bacteria that it's saying might have some high significance. It's hard to clinically make sense of that. Just in theory, and oftentimes, even with the information we have now treating vaginitis patients with recurrent issues. The symptoms are so non-specific, and sometimes takes a while to establish the diagnosis just because you're trying to figure out just having the presence of whatever you're picking up on with the diagnostic test is actually correlating to the symptoms and then the clearance of symptoms later. *(OB-GYN)*

3.4.2 Need for Further Testing to Understand Clinical Utility

In addition to the need for a greater understanding of the microbiome, participants across all groups stated that there is a need for further testing to understand the clinical utility of these microbiome tests. For example, analyses could be conducted on large datasets to develop an understanding of how the microbiome could be altered and the effects of these interventions. These types of studies may increase the understanding of how best to interpret and utilize microbiome results. Several participants explained:

> I mean you really have to have large population studies that can look at these microbiome and how altering these microbiome, the clinical trials, with how altering these microbiome has led to effective changes, how long are these changes, how long can you make any of these changes, we need so much more data before we can know this is a pre-Penicillin era of the microbiome. (*Gastroenterologist*)

> You need data, good data. So, you need to know first that your test is reproduce-able and reliable and then you need to have a study where a population is studied and an intervention is studied and a result is found. (*Gastroenterologist*)

> So, I think we need that level of expertise and science, so that we can, if I truly order a microbiome assessment and it tells me that this person is predisposed to autoimmune disease or this person has the obese genotype, it should be actionable. It shouldn't be that, "Well, it's only effective in 33% of the patients and so this is just like flipping a coin or this is nonsense." (*Gastroenterologist*)

3.4.3 Using Microbiome Test Results in Context

Unlike other physicians, those from the Functional Medicine group spoke of ordering microbiome tests as part of a panel of assessments for their patients. These tests provide one aspect of gut health and the immune system and are viewed in conjunction with a series of other tests to determine patterns and correlations, rather than used in isolation. These providers also emphasized that viewing test results without the context of the patient history and additional tests may be unhelpful, given the limited understanding of the microbiome, or misleading. As Functional Medicine physicians explained:

> Where I can get a better picture can really help me to triangulate or targeting and use the micro-biome as one aspect... If we're looking at something like complete blood count, we're not just looking at a one thing, we're looking at the pattern of what's going on, within that to understand

and while there are some individual aspects that can help us seeing the patterns across everything that gives us a bigger picture. *(Functional Medicine Physician*)

We know their history, we know what's going on, we have all of the other bloodwork, the metabolites, etc., that we use to put the results of the Micro-biome test into context and then that's where it becomes valuable to us as treatment. When it's used all by itself as the only thing that's being done, I think that that can be very misleading for people and could potentially cause... Depending on how its interpreted and recommended, that could potentially cause harm. *(Functional Medicine Physician*)

We recognize that only 1% of the stool is culture-able, but when we see some big shifts and imbalances and it's telling us that something is altered there. So, even though we're looking at a very small fragment, the microcosm is demonstrating something about the macrocosm and that's useful and we can see that here, but let's not over interpret what it means, until we have more data to be able to draw those correlations. *(Functional Medicine Physician*)

Table 6. Summary of Perceived Clinical Utility of Microbiome Tests Theme

Perceived Clinical Utility of Microbiome Tests	GI	Ped GI	Ob-Gyn	Functional Med
Limited Understanding of the Microbiome *Current state of the microbiome field, and how this affects clinical utility*	X	X	X	X
Need for Further Testing to Understand Clinical Validity *Importance of additional further testing, clinical trials, to assess clinical validity*	X	X		
Using Microbiome Test Results in Context *Viewing microbiome tests in context of patient history and panel of tests*				X

3.5 Regulatory Concerns of Microbiome-Based Diagnostic Tests

During the focus group, physicians across all groups were told that these microbiome-based diagnostic tests were virtually unregulated. Physicians were then asked to provide their thoughts on whether these tests should be regulated.

3.5.1 Privacy and Use of Data

When physicians were asked for their thoughts on regulation, participants in all groups indicated that they had privacy concerns and questioned the use of consumer data.

Privacy concerns of microbiome-based diagnostic test samples and data. In terms of privacy concerns, providers questioned who has access to test results and that DTC companies need to make their policies transparent for consumers. Although companies may own consumer data and samples, providers believed that these companies should be transparent about this to consumers so that consumers can make informed decisions about proceeding with testing.

> I think a lot of these, if I remember correctly, some of these places will maintain samples, and it's they then own the sample, and then they own the sequencing behind it. I think that's usually part of the deal. I don't know if there's any inherent risk associated with that at this time. But I think family should be aware of that and thoughtful about that, when they go into these. *(Pediatric Gastroenterologist)*

Concerns regarding selling consumer data. Some providers, particularly in the gastroenterology and OB-GYN groups were concerned about these companies selling consumer data to pharmaceutical companies and being targeted for advertisements.

> Yes, people should always be concerned about who has access to their medical results. Even if it's something as benign as a yeast infection, I don't know if that any woman wants to be then the target of yeast infection-centered advertisements or something like that. *(OB-GYN)*

> It would be really potentially devastating to be bombarded with information, different offers for treatment, things that you would otherwise not be like let the patient do that on their own time and not be confronted with that. *(OB-GYN)*

Concerns for insurance coverage. Providers in the gastroenterology group explained their concern that in the future, as scientists become more knowledgeable of the linkages between the microbiome and disease progression, insurance companies may use microbiome data to deny or limit insurance coverages for patients. Thus, regulatory safeguards will need to be in place to prevent this from occurring.

> Actually, I think probably eventually they should, because if different microbiomes that are associated with different types of longevity or disease patterns and when insurance companies or life insurance companies, etcetera, you know, it's pretty much like the HIV test or like HLA-B27 test, you don't want to ever check yourself at HLA-B27, because that's going to make you uninsurable for a lot of things forever. So, those might be some unintended consequences, where really if it is used, it should be used in the context of patients to improve their health, improve their wellbeing and how can it be altered and should not be used for any other third-party uses. *(Gastroenterologist)*

> Right now, if you do BRCA testing, you're positive, your insurance company can't say, "I'm going to charge you more, because you're higher risk of breast cancer," and that's illegal. So, I think the same way you have to extrapolate those protections to microbiome. *(Gastroenterologist)*

Concern for DTC companies collecting and aggregating consumer data. Several physicians, particularly those in the pediatric gastroenterology and functional medicine groups discussed concerns regarding microbiome and genetic testing DTC companies collecting data (microbiome samples and other demographic data) for their research or other purposes. Although this may be the standard in the

industry, physicians believed that this should be transparent to the consumer, so they are allowed to make informed decisions when moving forward with the test.

> I think I'm always a little concerned with this financial component and the direct consumer testing for not only microbiome but also 23andMe, like the DNA profiles. I mean, these are companies that have gone under scrutiny because of the use beyond just what the consumer is expecting. I assumed it was pretty standard practice that these companies are collecting this for metadata analysis, for their own purposes. So, my assumption, it would be the exception for a company to not use it for that. Are all patients aware of that? I don't know, I assume not, and what risk really is there, is something that I don't fully appreciate. If it's de-identified, are they at risk?...But that is something that I do hope that patients are thinking about. *(Pediatric Gastroenterologist)*

> I think it should be treated like any other medical information. It needs to be in a [inaudible] format and oftentimes, with say, director consumer companies, there's a lot of other information that are collected with just the microbiome results. Some of these companies will do questionnaires that ask a lot of information. So, I do think that there should be concern over who gets access to that. *(Functional Medicine Physician)*

Concerns for privacy and use of data may be more theoretical. Several participants, particularly those in the OB-GYN and pediatric gastroenterology groups also noted that although there are legitimate regulatory concerns for consumers, they may not an issue at the moment, as the microbiome field is still being explored. Until the science has established a connection between the microbiome and disease progression, these providers believe that these are hypothetical regulatory concerns.

> I mean, I think insofar as this information is sort of sensitive information, like gonorrhea, chlamydia, and they may not want their mom to know or whoever to know. Yes, I don't know that it's a genetic information issue. And I mean, I know there's all this stuff about how you can now fingerprint a person from their microbiome, I think it's more of the gut. But I think at present, that concern is more theoretical, I think it's more the standard sort of patient information concerns that would apply to any sort of sensitive information like gonorrhea, chlamydia test results. *(OB-GYN)*

> I think in general, as opposed to some of the concerns around releasing genetic testing, I don't think that these give enough information that would be a concern for access. *(Pediatric Gastroenterologist)*

3.5.2 Regulatory Aspects of Microbiome-Based Diagnostic Tests

Physicians across groups believed that there should be greater regulation for microbiome-based diagnostic tests. Several suggestions were provided, including ensuring regulation of patient health information, microbiome-based diagnostic test recommendations, and standardization and transparency of test validation processes. OB-GYNs also expressed concerns about use of DTC STI tests. Although the majority of physicians endorsed greater regulation, a few did not, stating that over regulation of microbiome-based diagnostic tests may impede innovation, and that these tests were a low priority issue.

Regulation of patient health information. Several participants in all groups stated that microbiome-based diagnostic tests require federal regulation, such as those that govern genetic tests. Physicians also stated that Health Insurance Portability and Accountability Act of 1996 (HIPAA), a federal law that required the creation of national standards to protect sensitive patient health information from being disclosed without the patient's consent or knowledge, should also apply to microbiome-based diagnostic test results.

> I've never actually thought about that DTC testing doesn't actually have to apply the same HIPAA guidelines that we employ as physicians. I'm not concerned about where that data goes as a physician in a HIPAA compliant ordering process that we go through and there may be deidentified data that is being used for data aggregation. I don't have a concern about that. I do have a concern about direct consumer testing where there aren't clear safeguards around that. I'm actually not even aware that that's an issue, but you're raising it. So, I guess it's something that it should be not unlike the concerns years ago about genomic data and being able to protect that. *(Functional Medicine Physician)*

> I would hope that a company would keep the information confidential, just like any other sort of laboratory that's out there. So, that's when they're talking about regulation, for all of these things. I feel like these companies should abide by some sort of rules, that all the other laboratories are required to follow. So yeah, I would hope that they would even disclose that if they do not have to follow the rules to let consumers know, and just be completely transparent and they're going straight to the consumer and they're allowed to do that. And I think that I mean, issues of autonomy, [consumers] can figure out themselves whether or not they want to proceed with the testing. But I would hope that there will be some sort of oversight. Because I believe that this is going to happen more and more in the future. *(OB-GYN)*

Regulation to standardize microbiome tests. Similar to discussions regarding analytical validity (Section 3.2.2), physicians raised suggestions to regulate the assays used and to standardize reference ranges for these tests. Regulating the process to identify and report microorganisms will help ensure the analytical validity of these microbiome tests, and thus, increase confidence in the findings of these tests.

> If we were certain of how to interpret accurate and valid data, then I think, yes, it should be regulated, because you want everything done in a reliable fashion, right? So, you can trust the data. And there's someone else looking in and making sure people are doing their job. *(Pediatric Gastroenterologist)*

> If this were ever going to be anything that we would use in our regular practice, it would definitely need to be more regulated. And like they were saying, I think that women with refractory vaginitis, they're a vulnerable population. A lot of women are would spend a lot of money on stuff like this. And just to think if we can't assure them of the quality of our product, I feel like that would be really irresponsible. *(OB-GYN)*

Regulation of microbiome-based diagnostic test recommendations. Physicians also suggested regulating the recommendations that accompany test results. This was more salient in the pediatric gastroenterology and OB-GYN. Recommendations could include a disclaimer stating that consumers should consult their physician before implementing new treatments. Physicians also discussed the concerns of DTC companies advertising treatments based on these recommendations, and the potential harms of these treatments.

> But from a recommendation standpoint, I think to make sure that the wording reflects where the research is, to say that our recommendations are based on our algorithm or some other type of thing that has not been FDA-approved, or some disclaimer to say, "Please, follow with your primary doctor or your GI doctor or something," because otherwise, it seems like, the way that it was read, the sample data we have, things very definitive. "This is how you should interpret this. You have these problems." And that I think is misleading. *(Pediatric Gastroenterologist)*

> Yeah, I think it would have to be very carefully marked...like “don't pursue treatment without discussing with your providers” something like that. *(OB-GYN)*

> But some regulatory body on the recommendations that those companies give based on those results I think would be helpful, not necessarily on the test themselves at this stage, because we don't know how to clinically interpret them. But the companies that are recommending things that we would consider harmful for patients, some kind of body to oversee that, I think it may be beneficial. *(Pediatric Gastroenterologist)*

Regulation of positive STIs results. A few OB-GYNs expressed the benefits of a DTC STI test, which can be conducted in private, is feasible, and may be considered less stigmatizing compared to traditional testing performed by an OB-GYN. These physicians, however, were concerned about positive tests for STIs, how this is reported in public health systems, and if partner tracing is conducted.

> And the one other thing I was going to bring up is just if you get into STIs, then a big question is, does this result actually go to somewhere where it's reportable? And what about partner treatment or tracing? And that's really the biggest issue. I mean, partner treatments, a big issue, regardless for STIs but for syphilis in particular, that is supposed to be contact tracing, you're supposed to go find the person and all their partners and stop the syphilis outbreak. So, I think that's a big concern, will these results get reported or not? *(OB-GYN)*

> If you want to order your vaginal microbiome or your gut microbiome and you just want to figure out what it is, I think that's fine. But I think with the STIs, I think if there were better regulated there, maybe it's a potential, another space another way for people to get better access to testing, it's probably less stigmatizing, easier for patients to go and access. And so, I think there's potential, it just has to be done properly, because the stakes are not inconsequential. *(OB-GYN)*

Need to balance innovation and regulation. Despite the majority of participants’ concern about regulation, a few physicians discussed the need to ensure that regulation does not stifle innovation. Some physicians stated that rather than enforcing regulation, companies should be transparent about their processes, providing physicians and consumers with enough information to make an informed decision about the test.

> Being able to say, "Okay, be transparent about what your algorithm is that's underneath it. If it's published, then you're your first to market, you can do that and you can demonstrate it and people can question it and look at it." That's what I'd like to see, as an opportunity. I'm getting I think maybe a little far afield here, but trying to put FDA approval on each of these kinds of stool

> tests is something that it just shut down, it would make it completely unavailable. *(Functional Medicine Physician)*

> Because I don't want to overregulate something so that companies feel like they cannot like innovate and make anything because there's too many rules. And I just think about just working in a large healthcare system with some of the regulations, there's a lot. And I think sometimes the regulations can actually get in the way of creativity and moving the field forward. So, part of this definitely, for the things that can impact other people. And for safety concerns, but you want to know about your vaginal microbiome and you want to spend the money and that's up to you. I don't think that part would have to be particularly regulated until we learn more about it and sort of what it means. *(OB-GYN)*

Regulation for microbiome-based diagnostic tests is a lower priority issue. For some physicians, the regulation of microbiome-based diagnostic tests was considered a lower priority issue. This was more salient in the pediatric gastroenterology groups. These physicians reported that the lack of regulation for supplements, holistic treatments, or known harmful substances was a greater concern compared to microbiome tests.

> I think there are probably a lot of other things that I would choose to regulate first that are more harmful, like these supplements, probiotics. Things that a lot of the bodybuilders do, then we see a lot of kids coming in using supplements and body enhancers and using a lot of things that are questionable there. I worry more about things with hormones in them or things with creatine or arsenic. And so, should they be available? Probably not. Would I make that a big priority? Probably not. I would probably target the things where the patients are actually getting exposed to something that's harmful. We probably should start with getting rid of cigarettes and other substances that we know are harmful that people still choose to use. We don't regulate well enough. *(Pediatric Gastroenterologist)*

3.5.3 Consumer Access to Microbiome-Based Diagnostic Tests

Participants were asked whether microbiome-based diagnostic tests should only be accessible to patients via physician order or if DTC may be an acceptable option.

Preference for tests to be accessible by physician order. Participants across all groups believed that given the concerns of analytic validity, difficulty with interpreting the test results and potential harms of the recommendation, tests should be accessible by physician order. If these tests were properly regulated and standardized, providers may feel differently about the DTC aspect.

> If consumers are given information that's usable directly to them and it's not misleading, etc., that's a great thing. You don't need to get somebody in the middle of that. That I think is the issue here is just, it has to be in some way valid and reliable information, which I think we've expressed some concerns with the mock example that we've got. *(Functional Medicine Provider)*

Interpreting results with provider. Several physicians across groups suggested in order to reduce confusion and utilizing potentially harmful treatments, microbiome-based diagnostic test results should be interpreted by a provider. This was viewed as a compromise by some providers, who acknowledged

the plethora of DTCs on the market, and the benefits of patients' access to their data, but sought a way to ensure the safety of patients.

> I think in a perfect world a patient couldn't order a test that they couldn't interpret on their own or take to a healthcare professional that could be easily interpreted to help their health. *(Gastroenterologist)*

> I believe that the consumer should have the right to be able to see this information if they're interested in it. I do believe, strongly though, that everything that the consumer receives has to be engaged with a strong recommendation to interpret and discuss what to do about these results with a trained provider. But the movement right now is towards consumers having access to results, being able to request information about their own bodies, we've been empowering them. So, Quest labs and other labs allow you to send allergy testing and things like that by yourself, if you pay out of pocket. So, I mean, if this is the direction that we're going, I don't necessarily think we should treat this any differently. But no one should be interpreting allergy results just like they should not be interpreting these results without actually talking to someone who knows how to interpret it. *(Pediatric Gastroenterologist)*

> If we start seeing these tests can become more prevalent in practice, it might be important to be proactive and talk to patients and say, "Hey. If you're thinking about getting this test, come talk to us about it, or come talk to whoever your provider is about the results because it may be difficult to interpret without additional information." *(OB-GYN)*

Table 7. Summary of Regulatory Concerns of Microbiome-Based Diagnostic Tests

Regulatory Concerns of Microbiome-Based Diagnostic Tests	GI	Ped GI	Ob-Gyn	Functional Med
Privacy and Use of Data				
Privacy concerns of microbiome-based diagnostic test samples and data	X	X	X	X
Concerns regarding selling microbiome data	X		X	
Concerns for insurance coverage	X			
Concern for DTC companies conducting research on consumer data		X		X
Concerns for privacy and use of data may be more theoretical		X	X	
Regulatory Aspects of Microbiome-Based Diagnostic Tests				
Regulation of patient health information	X	X	X	X
Regulation to standardize microbiome tests	X	X	X	X
Regulation of microbiome-based diagnostic test recommendations		X	X	
Regulation of positive STIs results			X	
Need to balance innovation and regulation			X	X

Regulatory Concerns of Microbiome-Based Diagnostic Tests	GI	Ped GI	Ob-Gyn	Functional Med
Regulation for microbiome-based diagnostic tests is a lower priority issue		X		
Consumer Access to Microbiome-Based Diagnostic Tests				
Preference for tests to be accessible by physician order	X	X	X	X
Interpreting results with provider		X	X	X

Appendices

Appendix A - Physician Focus Group - Microbiome Moderator's Guide

[NOTE: The Moderator Guide consists of possible questions that researchers anticipate are relevant to ask. However, this does not mean that every question listed will definitely be asked. As per standard protocol for focus group research, researchers will allow the conversation to unfold naturally. Certain questions listed may not be asked because they may no longer be relevant to that particular discussion, or time constraints may not permit.]

Moderator: Welcome and thank you for coming. My name is [insert moderator name] and we also have [insert co-moderator/assistant's name] here with us. I am going to give everyone an overview of what we will be doing for the next hour. As you know from the information sheet you were given, we are interested in learning more about healthcare providers' knowledge and attitudes toward testing for gut and vaginal microbiomes. We'll be asking you to talk about what you think about these tests, and we'll ask you to interpret some mock test results. There are no right or wrong answers to our questions. We want you to answer honestly, including letting us know if you don't know how to answer a question.

Before we start, we ask that you silence your cell phones. We want to hear from each person, so if you are talking a lot, let others talk for a little while too. Our goal is not to get everyone to agree or disagree. It is about hearing each person's unique opinion.

Please just use a first name to refer to yourself (we will use a code in our study records instead of your name). We ask that you not disclose personal information with us that you are not comfortable sharing. Anything you tell us will be kept private. We also ask that everyone who takes part in the discussion group keeps whatever we talk about completely private. We want to be sure you are comfortable in what you choose to discuss with us. Please let us know if you have any questions or concerns. We appreciate your honest answers to questions, including letting us know if you don't know how to answer a question. In a focus group, it's important to express yourself openly. There are no right or wrong answers. We simply want to know what you think. I would like everyone to be a part of this conversation. You do not need to wait for me to call on you to talk, but only one person should speak at a time.

We will be recording this discussion for research purposes. Are there any questions before we begin? [If yes, answer questions, if no, proceed]

We will ask you to say your first name before speaking. If you would prefer not to identify yourself, you can use a different name. Since this discussion is being recorded, saying your name will help us identify who is speaking when we listen to the recording later on. The only people who will hear the tape or see the written record are the researchers working on this project.

[Moderator may elicit elaboration on questions below via prompts such as, "Tell me more about that," and "can you give me an example of what you mean?"]

Question 1. What is your experience with microbiome-based diagnostic tests? Probe: Have you ever seen any such test results? Have any of your patients brought them to you?

Question 2. Have any of you ever ordered one of these tests? If you have ordered these tests, why did you do so? (Additional Probe: Did patients ask you to do so? Did you think that the results would provide information that would affect treatment decisions? If so, did the results inform your treatment decisions?)

Question 3: How would you describe your attitude generally towards alternative/complementary/ integrated medicine?

Question 4. Do you think these microbiome tests will affect treatment decisions?

Question 5. Do you have any concerns about their use with patient populations? (Additional Probe: Do you think there are any harms associated with these tests? If so, what are they?)

Question 6. Do you think patients should be concerned about who gets access to their test results? If so, why?

Moderator: At this point we would like discuss the mock test results that were emailed to you. If you would like to discuss a particular finding, we can bring that up on the screen.

Question 7. How would you describe what the findings of this test reveal?

Question 8. How would you interpret this test's clinical validity, reliability, and utility to clinicians and consumers?

Question 9. What further information (if any) would you want to know to help you interpret this test?

Question 10. Do you think these tests should only be accessible to patients via physician order?

Question 11: Do you consider these tests an advancement of modern medicine or would you consider them to be more of an alternative/complementary medicine?

Question: 12: These tests are virtually unregulated. Do you think they should be more heavily regulated? Why or why not?

Moderator: That is all the questions we have for you. Do you have any questions for us or anything to add that we haven't already discussed? [If no, close, if yes, follow-up]

Thanks so much for taking the time to talk to us today. Feel free to contact us if you have any further questions.

Appendix B - Regulation of Microbiome-Based Diagnostic Tests - Codebook

Parent/Child Code	Description	Notes
1. Experience with consumer tests	Experience with tests either as a provider ordering for patients, or as a consumer	
a. Awareness of microbiome tests	Comments re: provider or consumer awareness of microbiome tests, even if they have not previously used them	
b. Order/request microbiome tests	Comments from providers or consumers about ordering/requesting microbiome tests. Can be hypothetical responses to requests.	
c. Consumer genetic tests	Experience with genetic tests, such as ancestry.com and /or 23andme	
d. Other	Other comments that relate to experience with consumer tests	
2. Perceptions of microbiome tests	Perceptions of tests, including usefulness, validity, and medical disciplines, understandability of results, harms/benefits	Stratify by medical discipline
a. Clinical utility	Discussion re: if tests help with treatment decisions or lead to improved health outcomes	

Parent/Child Code	Description	Notes
b. Clinical validity	Discussion re: accuracy of test, ability to accurately identify or predict a disease or health condition	
c. Education tool	Comments from physicians who believe microbiome tests can be used as an educational tool for patients	
d. Modern medicine vs integrative medicine	Whether microbiome tests are examples of traditional modern medicine or alternative/complementary/integrative medicine	
e. Interpretation	Comments re: perception of ease or difficulty of interpreting test results	
i. Over specificity	Comments re: results focusing on specific species rather than the larger microbiome	
ii. Use in context	Discussion re: importance of viewing the tests results within the context of the patient's history and other tests	
iii. Lack of understanding to interpret data	Lack of understanding in the field of how interpret findings, meaning of findings for clinical use	
iv. Lack of belief in tests	General disbelief of microbiome tests and field of study (not only limited to questioning clinical validity)	
f. Benefits	Perceived benefits of microbiome tests	
g. Harms	Perceived harms of microbiome tests	

Parent/Child Code	Description	Notes
h. Costs	Costs consumers are willing to spend on microbiome tests	
i. Other	Other comments that relate to perceptions of test	
3. Motivations for testing	Providers and consumers' motivations to order tests	
a. Microbiome tests	Motivations specific to microbiome tests	Code may include discussion of consumers' past experience with similar tests, satisfaction/dissatisfaction with their diagnosis and treatments leading them to request tests. May need to create more grandchild codes once analysis begins
b. Genetic tests	Motivations specific to consumer genetic tests	
c. Other	Other comments that relate to motivations for ordering or requesting tests	
4. Attitude towards integrative medicine	Providers and consumers' attitudes towards alternative/complementary/integrative medicine	May need to create more child codes once analysis begins
5. Understanding sample results	Providers' and consumers' understanding of sample test results	

Parent/Child Code	Description	Notes
a. Interpretation	Comments re: how to interpret the test's clinical validity, reliability, utility and information needed for further interpretation	Code may include information re: content, range, relevant/irrelevant scientific information, which affects interpretation. May need to create more grandchild codes once analysis begins
b. Understandability	Discussion of whether results were easy or difficult to understand, what information needed to be clearer	May include discussion of format, volume of information that affects understandability. May need to create more grandchild codes once analysis begins
c. Other	Other comments that relate to understanding test results	
6. Regulatory issues		
a. Privacy	Discussion of privacy concerns, who has access to test results	
b. Data security	Discussion of data security concerns	
c. Use of data	Discussion of any concerns re: use of data, including possible insurance implications, discrimination, use for company's own research	
d. Availability of tests	Discussion whether tests should only be accessible to patients via physician order	

Parent/Child Code	Description	Notes
e. Thoughts on regulation	Comments re: benefits or concerns about regulation, including how regulation can lead to better tests	
f. Claims of tests	Comments re: quality or usefulness of tests, claims, truthfulness	
g. Recommendations	Any comments pertaining to recommendations including a disclaimer, or the need to regulate recommendations	
h. Validity	Comments re: need to regulate test results, determine validity	
i. Healthcare provider responsibility	Comments of how providers should be have formal responsibility for interpreting results, especially if ordering tests	
j. Balance innovation and regulation	Comments re: need to not let regulation hinder research and development	
k. Interpreting results with provider	Comments re: need for patients to review test results and recommendations with a provider, even if patient has ability to purchase test on their own	
l. Other	Other comments that relate to regulatory issues	
7. Satisfaction with medical services	Consumers' comments re: satisfaction with medical services/treatments that they have received	Determine if this relates to "motivation for testing" codes during analysis. May need to create

Parent/Child Code	Description	Notes
		more child codes once analysis begins.
8. Interesting Quotes	Any interesting, rich quotes that may be helpful for analysis or reporting	
9. To Discuss	Any quotes that need further deliberation, unsure of where to code	