Meeting Report

First meeting of the working group convened for the NIH-funded grant:

Regulatory Framework for Direct-to-Consumer Microbiome-Based Tests

June 16–17, 2021

Investigators

- Diane Hoffmann, Law & Health Care Program, University of Maryland Carey School of Law (Principal Investigator)
- Dr. Frank Palumbo, Center on Drugs and Public Policy, University of Maryland School of Pharmacy
- Dr. Jacques Ravel, Institute for Genome Sciences, University of Maryland School of Medicine
- Dr. Mary-Claire Roghmann, Department of Epidemiology and Public Health, University of Maryland School of Medicine
- Dr. Erik von Rosenvinge, Division of Gastroenterology, University of Maryland School of Medicine and Veterans Affairs Maryland Health Care System

Background

In August 2019, Diane Hoffmann and co-investigators from the University of Maryland Baltimore were awarded an R01 grant from the National Human Genome Research Institute (NHGRI) to study the regulatory framework for direct-to-consumer (DTC) microbiome-based screening tests. These tests rely on genomic sequencing technology and are available to consumers without a provider prescription. The goal of this four-year grant is to inform regulatory approaches for DTC microbiome-based tests and to identify and address regulatory problems and gaps and encourage a balance between regulation and innovation in the microbiome-based testing industry.

The microbiome consists of microbial communities residing in various niches of the human body, including the gut, vagina, and skin. As evidence grows to suggest that the microbiome plays an important role in a variety of health conditions, interest in commercializing the diagnostic and therapeutic potential of profiling an individual's microbiome has increased. Although the DTC microbiome-based testing industry is poised to expand exponentially in the next ten to twenty years, the microbiome is still an active area of research, and the medical applications for microbiome-based tests have not been conclusively determined.

For DTC products, there is concern that consumers will be misled by claims that are not supported by independent research and harmed by test results that they do not understand and may use inappropriately. Similarly, providers ordering these tests or receiving test results from their patients may have insufficient expertise to interpret results and may rely too heavily on the recommendations of the commercial laboratories marketing these tests. Further, there are research ethics concerns regarding consumer informed consent and the extent to which consumers understand the privacy implications of providing health information to commercial entities.

The rapid growth of the DTC microbiome-based testing industry necessitates a regulatory response that balances safety, quality/accuracy, access, and privacy of consumers with value to health care decision making and innovation within the industry. Similar to initial advances in genetic testing technologies, there is a clear need to assess the benefits and risks of these tests and to examine current regulatory frameworks governing them.

The Project

The study team established a working group of approximately 30 expert stakeholders including scientists, clinicians, bioethicists, academics, lawyers, a consumer advocate, and individuals from the microbiome-based testing industry. In addition, representatives of FDA and FTC were invited to participate. The full working group list is attached as Appendix A.

The purpose of the working group is to assess the current regulatory framework for DTC microbiome-based tests and to develop recommendations for the regulatory approach to these products going forward. Specifically, the working group will explore, among other things, whether potential regulatory frameworks (1) ensure that patients receive accurate information about their microbiome; (2) ensure that information provided by DTC microbiome-based tests has analytical and clinical validity, and some utility for patients; (3) ensure that patients and providers have a clear understanding of the potential uses of patient samples in research; (4) provide oversight of companies that are actually conducting human subjects research when collecting large volumes of patient/consumer data; and (5) encourage an appropriate informed consent process that outlines potential risks to privacy. Working group members will also share views about the "ideal" regulation of DTC microbiome-based tests and how these tests should be used.

Three working group meetings are planned over a two-year period. On June 16–17, 2021, the study team convened the first working group meeting. The agenda for the meeting was informed by the work already completed under the grant and is attached as Appendix B. Due to the COVID-19 pandemic, the two-day meeting was held remotely over Zoom, and included presentations, small group discussions, and participant polling. Presentations and polling results from the working group meeting are recorded and available for viewing on the project website.

Prior to the first working group meeting, participants were asked to review research thus far completed under the grant which included a DTC microbiome-based testing industry and regulatory landscape analysis. At the meeting, participants also heard the results of several focus groups and interviews with microbiome experts, patients, and clinicians that the study team conducted during the year prior to the meeting. The meeting featured presentations on the current state of microbiome science and the DTC microbiome-based testing industry, potential regulatory oversight of microbiome-based tests, the industry's roots in DTC genetic testing, and test quality terminology. The meeting concluded with a presentation on test quality standards under the Clinical Laboratory Improvement Amendments (CLIA) and their application to DTC microbiome-based tests.

During the meeting, working group members participated in small group discussions, i.e., Breakout Sessions. Members were divided into groups of 7–8 and each group included a mix of substantive expertise (e.g., science, law, and bioethics) and perspectives (e.g., research, industry, and clinical). Each small group discussion was facilitated by a member of the study team and explored four topics areas earlier covered in the meeting presentations. Finally, on both days of

the meeting, working group members were polled regarding their opinions about the benefits and risks of microbiome-based testing and whether regulation of these tests should be required.

The First Day

1. <u>State of the Science</u>

The first day of the working group meeting began with three presentations about the current state of the science of the microbiome. The first two presentations focused on the gut and vaginal microbiome, respectively, and addressed the following questions:

1) Is there a core/healthy microbiome?
2) What is the relationship between the microbiome and health/disease?
3) What are the diagnostic and predictive potential of the microbiome, and what will the future bring?
4) What are the knowledge gaps?

The third presentation focused on the microbiome as it relates to diet and nutrition and addressed the following questions:

1) What do we know about the relationship between the microbiome and diet/nutrition and dietary supplements?
2) What are the knowledge gaps?

Dr. Alexander Khoruts, Professor of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, talked about the diagnostic potential of gut microbiome tests. He began by stating that although it is unclear whether microbiome tests can currently evaluate the risk of disease or predict better health, due to their frustration with traditional medicine, some patients have pursued their own microbiome testing and demanded treatment from their providers based on the results.

Gut microbiome testing can identify pathobionts (i.e., organisms that are associated with disease) and commensal organisms (i.e., a diverse community of organisms associated with health). The identification of pathobionts may lead to microbiome-based diagnostics for managing gut-related diseases (e.g., risk of colon cancer, response to IBD therapy, and staging of liver disease). For gut health management, however, there is no universal agreement about what constitutes healthy commensal diversity and normal ranges for individual member microbial species do not exist.

Microbial diversity at the population level is characterized by enterotypes of mutually exclusive communities of microbes that reside in the gut. Common gut enterotype classifications consist primarily of either *Bacteroides* spp., *Ruminococcus* spp., or *Prevotella* spp. Loss of *Prevotella* is observed at the population level in industrial societies where diets high in processed foods and antibiotic usage cause reduced microbial diversity. Loss of *Prevotella* at the individual level, however, is not necessarily associated with dysbiosis. Instead of classifying normal gut inhabitants by enterotype, a better method of determining what constitutes healthy microbial diversity might be to build association networks across microbial communities using machine learning, i.e., artificial intelligence.

Dr. Khoruts states that commercial microbiome testing currently offers no benefit to the consumer because an individual's microbiome is dynamic over time and many samples are required to obtain an objective readout of gut health. Perhaps, with the right incentives and

regulation, development of useful microbiome diagnostics to guide gut health programs is conceivable. Regarding clinical microbiome-based diagnostics for gut disease management, however, these are coming, and some may already be here. Dr. Khoruts' PowerPoint presentation may be found **here**.

Dr. Jacques Ravel, Professor and Associate Director for Genomics, Institute for Genome Sciences, University of Maryland School of Medicine, discussed the state of the science in our understanding of the vaginal microbiome. Unlike the gut microbiome where a healthy microbiota is associated with diversity, the "healthy" vaginal microbiome is thought to have relatively few bacterial species. In reproductive age women, *Lactobacillus* spp. are often characteristic of an optimal vaginal microbiota, and their absence is now recognized as a non-optimal vaginal microbiota.[1]

Lactobacillus is a genus of Gram-positive, facultative anaerobic or microaerophilic, rod-shaped, non-spore-forming bacteria. The *Lactobacillus* spp. found in the vagina are *L. crispatus*, *L. gasseri*, *L. jensenii*, and *L. iners*. The loss of *Lactobacillus spp.* is an ecological disturbance of the vaginal microbiota that can cause discharge, itching, odor and/or pain. This shift in composition and structure of the vaginal microbiota is also associated with an elevated vaginal pH and the presence of facultative and strict anaerobic bacteria including *Gardnerella vaginalis* and *Atopobium vaginae*. The consequence of these vaginal changes are vaginitis or bacterial vaginosis (BV), and they are the most common reasons for patient visits to an OB/GYN. BV is traditionally diagnosed using clinical (e.g., signs and symptoms) and microbiological (e.g., microscopy) methods and is primarily treated with antibiotics but recurrence is common.

Using gene sequencing, the vaginal microbiota is characterized into one of five community state types (CST) that differ in their microbial composition and abundance. Based on the analysis of over 13,000 samples, BV is associated with CST IV which lacks *Lactobacillus* spp.; however, not all CST IV result in BV. Although the microbiological definition of BV aligns well with CST IV, the clinical definition of BV still requires clinically evaluated signs and symptoms. Considering that only half of women with CST IV vaginal microbiota report symptoms of BV, providers are not treating the risks associated with CST IV (e.g., pelvic inflammatory disease, acquisition of STIs, and preterm delivery/low birth weight) but only the symptoms of BV.

There is no accepted molecular definition of BV, and without a molecular definition, microbiome-based diagnostics for BV cannot easily be implemented and validated. Although a molecular definition of BV is desperately needed, the lack of efficacious treatments for BV limits the clinical impact of any expanded definition. Dr. Ravel's PowerPoint presentation may be found **here**.

Dr. Suzanne Devkota, Assistant Professor, Cedars-Sinai Division of Gastroenterology, spoke about the relationship of diet to the gut microbiome. Microbes colonize the gut based on

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[1] Vaginal microbiota lacking *Lactobacillus* spp. are mostly observed in black and Hispanic reproductive-age women. Consequently, vaginal microbiota are preferentially referred to as optimal/non-optimal rather than health/unhealthy to avoid creating a different "normal" based on race. *See* Amber Benezra, *Race in the Microbiome*, 45 SCI., TECH., & HUM. VALUES 877, 885–86 (2020), https://journals.sagepub.com/doi/pdf/10.1177/0162243920911998.

where their function is best suited; hence, in health—form follows function, and, in disease—it is survival of the fittest.

Given that gut microbes live where they are best suited, the question becomes whether changes in diet can modify the gut microbiome and thereby improve health. At the population level, there are distinguishing gut microbiota compositions attributed to distinct dietary patterns. At the individual level, however, the same diet often does not lead to the same microbiota composition or functional response, i.e., two individuals can eat the same diet and not have the same gut microbiota. Algorithms have been successful at predicting an individual's microbiome or biological response to foods based on that individual's own historical data, but not across populations.

At the population level, studies show that there are clear microbiome composition differences in industrialized versus non-industrialized regions. At the individual level, nearly every human diet study notes large inter-individual variations in microbiomes. However, the vast majority of these studies are small, focus on one geographic region, and do not control for other lifestyle factors (e.g., incomplete food diaries). Although in-house studies may help combat some of these problems, such studies are expensive and external (i.e., environmental) influencers of microbiome composition and function cannot be ignored.

The NIH *All of Us* precision health study is exploring nutrition as its first ancillary study and will reduce the effects of problem data by being large (i.e., 10,000 participants) and including both a free-living, controlled feeding study and an in-house, controlled feeding study. The objectives of the research are to (1) examine individual differences observed in response to different diets by studying the interactions between diet, genes, proteins, microbiome, metabolism, and other individual contextual factors; (2) use artificial intelligence to develop algorithms to predict individual responses to foods and dietary patterns; and (3) validate algorithms for clinical application. Dr. Devkota's PowerPoint presentation may be found **here**.

2. Industry Initiatives

Next, the working group heard from two microbiome researchers who have been involved in the establishment of microbiome-based testing/profiling companies -- **Dr. Christopher Mason, Professor of Physiology and Biophysics, Weill Cornell Medicine & Co-Founder of Onegevity**, and **Dr. Eran Elinav, Weizmann Institute of Science & DayTwo**. Diane Hoffmann, the Project PI, asked the two researchers the following questions:

1) Please tell us a little bit about your company and why you started it?
2) How would you describe your business model?
3) What kind of recommendations do you give to your customers?
4) How do you develop your recommendations?
5) How are you validating your recommendations? Have you made this publicly available through publication?
6) Are you building your own data bases? If not, where are you getting your reference microbiome data?
7) Have you developed your own software to analyze the data you collect? Does it require specialized personnel to use the data/analyze the data?

8) Do you address privacy in your Terms of Service?
9) Are your labs CLIA certified?
10) Do you think you are over-regulated or under regulated?
11) What are your most significant challenges as a company?

Dr. Elinav studies dietary influences on the gut microbiome, and his work led to the creation of the DayTwo company. Dr. Elinav's team at the Weizmann Institute developed a predictive algorithm that makes data-driven, personalized dietary recommendations to help prediabetic patients improve their glycemic control. This breakthrough algorithm shifts the paradigm from an emphasis on the foods of a healthy diet to the patient's response to food. Also, the ability to optimize an individual's diet avoids overly restrictive diets and induces better compliance. The algorithm uses blood sugar as a proxy for glycemia and provides a continuous measure of metabolism to facilitate machine learning.

Dr. Elinav's team subsequently confirmed the algorithm in a large-scale (i.e., over 100,000 participants), one-year randomized controlled trial that showed the gut microbiome plays a large role in the predictive capacity of the algorithm. The trial also demonstrated that, although patients' microbiomes changed substantially as a result of the algorithm-recommended personalized diets, the algorithm, itself, did not require adjustment. Dr. Elinav noted that the predictive algorithm functions as a black box, and they do not attempt to understand how these dietary modifications successfully control glycemia.

Dr. Elinav conducts his work independently of DayTwo's day-to-day operations. The DayTwo business model was limited to direct to consumer sales when it was a startup company in Israel but now includes business to business sales in the U.S. The large reservoir of microbiome data derived from the over 100,000 participants in the year-long clinical trial may also lead to more business for the company. The DayTwo lab is CLIA-certified. Dr. Elinav feels that current regulatory mechanisms cannot adequately assess big data/machine learning because, by definition, such algorithms are constantly evolving and cannot be "frozen in time" to facilitate validation.

Dr. Mason launched Onegevity in 2018 after collecting data from environmental and integrative genomics that emphasized the effect of diet on epigenetics. The startup company obtained venture capital and began offering multiomic profiling (e.g., microbiome-based testing combined with genetics testing) with a focus on the gut. Onegevity makes dietary recommendations and, now that it has been acquired by the Thorne company which manufactures probiotics, provides custom probiotics to consumers.

Dr. Mason's team conducted several studies including a stool collection validation study and a trial to validate Onegevity's test recommendations on patient cohorts (e.g., IBS/IBD patients). Dr. Mason notes that the best way to validate Onegevity's tests is to study hundreds/thousands of patients while independently replicating the results in different cohorts from different geographic regions. This, however, is very expensive.

The Onegevity lab is CLIA-certified. Over the past ten years, experts have offered recommendations to FDA about how to regulate big data/machine learning, but FDA is just now considering this issue. Dr. Mason feels that the current extent of regulation is adequate, but the future challenge for regulation is that, with few diagnostic tests on the market capable of

measuring the proportion of species in a sample and no guidelines for their use, validating these tests will be difficult.

3. Review of Sample Test Results

Just prior to the first small group discussion, i.e., Breakout Session #1, **Dr. Erik von Rosenvinge, Associate Professor, University of Maryland School of Medicine**, reviewed examples of the types of test reports that consumers receive from DTC microbiome-based testing companies. Dr. von Rosenvinge reviewed two gut microbiome test reports from the companies Viome and Thryve and one vaginal microbiome test report from the company Juno Bio.

Like most of these types of reports, the Viome report begins with a disclaimer that the information is only for educational purposes and the advice of a health care provider should be sought for diagnosis and treatment. The Viome report gives personalized scores (e.g., "needs improvement"; "average"; or "good") for twenty parameters related to digestive health. In this report of a hypothetical consumer, the inflammatory activity parameter is scored as "needs improvement." The report explains that the score is based on a reference range developed using a proprietary algorithm that incorporates functional and taxonomic components, but it does not state specifically how the reference range was determined. The hypothetical report also scores and interprets parameters for digestive efficiency, gas production, and metabolic fitness, but it provides a vague interpretation of what each score means relative to the parameter that is being measured. Finally, the report provides dietary and supplement recommendations. As an example, the report recommends eating more apples and eating less broccoli and includes an explanation for why the company claims that eating more apples and avoiding broccoli may improve the consumer's microbiome scores.

The Thryve report also begins with a disclaimer, and this is followed by an overview of the hypothetical consumer's scores (e.g., "optimal"; or "requires opinion") in six metabolic categories. As an example, this report scores carbohydrates in the category of nutrient absorption as "requires opinion" because the score falls outside of their reference range. The report also describes what the company believes each score means and provides recommendations for dietary modifications and supplements. Finally, the report gives probability ratios for the likelihood of this consumer having a specific condition or disease such as food intolerance or inflammatory bowel disease. The probability ratio range extends from improbable to more probable on a five point scale, but no validation of the ratio range is provided.

The Juno Bio report identifies the community state type (CST) of the hypothetical consumer's vaginal microbiome, explains the CST, and lists the five most abundant organisms found in the sample. This report recommends longitudinal (i.e., repeat) sampling and advises the consumer to book an appointment with a company "vulvovaginal specialist" to discuss the test results. Dr. von Rosenvinge's PowerPoint presentation may be found **here**.

4. Breakout Session #1

For this breakout session, Attitudes about DTC Microbiome-Based Tests, the working group members were asked the following six questions:

1) What benefits, if any, do you think these tests can provide to patients/consumers?
2) What risks do you see for patients/consumers in ordering these tests?
3) What questions, if any, would you have about the test results these companies provide if you received them?
4) What concerns do you have (or would you have if you had ordered one of these tests), if any, about the use of the information from your test results by these companies?
5) Do you think these tests should be available to patients without authorization from a physician? Why or why not?
6) These tests are virtually unregulated by FDA or other government agencies. Do you think they should be more regulated than they are? Why or why not?

Working group members found little benefit to microbiome-based tests, except that they empower patients/consumers who want to take control of their health. Further, patients seek out the tests as a possible solution where traditional medicine has failed them. By contrast, some working group members identified numerous risks of these tests. Chief among these were that (1) there is not robust evidence that test recommendations are clinically actionable, (2) vulnerable patients are susceptible to predatory marketing, and (3) patients may improperly self-medicate or avoid seeking definitive care from a provider based on the test results.

The working group wanted more information from DTC microbiome-based testing companies about the methodology of these tests and the algorithms and reference ranges used to make recommendations from the test results. Further, some working group members questioned the privacy of consumer test data and its use by the companies in follow-on research studies.

Working group members wanted physician authorization of these tests if they are used to diagnose a condition but not if they are used to provide general diet/health information. They also thought that these tests should be regulated but were unsure about the type of regulation. Some members drew the regulatory line at whether the tests are used for diagnostic purposes, other members focused on regulating company claims through test labels, and one member mentioned CLIA certification of DTC microbiome-based testing labs.

5. Focus Group and Interview Results

Immediately after Breakout Session #1, **Felicia Langel, Research Coordinator, University of Maryland Carey School of Law**, presented a summary of the results of the eleven focus groups and eighteen interviews that the study team had conducted over the prior year. The purpose of the focus groups and interviews was to understand how microbiome researchers, health care providers, and patients and consumers perceive DTC microbiome-based tests. All focus groups and interviewees were asked the same questions that the working group members were asked in Breakout Session #1:

1) Benefits of microbiome-based tests.
2) Risks of microbiome-based tests.
3) Physician/consumer questions about the test results.
4) Concerns about the use of information from the test results.
5) Physician authorization required/not required to order the tests.
6) Extent of regulation necessary/appropriate for the tests.

Several focus groups consisted of physicians from relevant specialties (e.g., gastroenterologists; obstetrician-gynecologists; etc.) divided into groups based on their specialty. Focus groups of consumers (not necessarily patients) were divided into groups based on whether or not they had ordered a DTC microbiome-based test, i.e., tested or untested. The interviewees were either physicians from relevant specialties, researchers with expertise in the gut or vaginal microbiome, or consumers who had ordered or might be interested in ordering a microbiome-based test and belonged to a patient population (e.g., IBD patients). A detailed report of the results of the focus groups and interviews is attached as Appendix C.

Physicians across most groups and most consumers felt that DTC microbiome-based tests offered patients/consumers a benefit by empowering them to request and obtain access to their personal health data. Consumers, alone, felt that test results could provide baseline data on a patient's microbiome which could be reassessed over time and correlated to changes in treatment regimens or dietary modifications. Regarding risk, all physicians and researchers were concerned that patients would use these tests to self-medicate and that these tests may indicate/recommend a patient should address a specific microorganism which may not have clinical relevance. Consumers, for the most part, did not identify any risks to these tests.

Physicians across all groups questioned the analytical validity of microbiome-based tests (e.g., lack of standardization; uncertain reference ranges), and most physicians and researchers questioned the degree to which microbiome-based tests can accurately identify or predict a risk of disease or other outcomes, i.e., clinical validity. Physicians across all groups and a few consumers were concerned about data privacy, but several physicians and consumers noted that privacy concerns may not be an issue at the moment because the microbiome field is still being explored. Until the science has established a connection between the microbiome and disease progression, these participants believed that privacy concerns are hypothetical.

Most physicians felt that these tests should only be accessible by physician order; while most consumers believed that the public should be able to purchase these tests directly and without a physician order. Several physicians, researchers, and consumers felt that, at the very least, test results should be interpreted by a provider. Many participants agreed that there should be some type of regulation of DTC microbiome-based tests, but there was no unanimity concerning the type or extent of regulation. For some physicians, researchers, and consumers, these tests have a low risk of harm and, therefore, do not need to be regulated. Felicia Langel's PowerPoint presentation may be found **here**.

6. Polling Questions – First Day

Working group members completed a set of eleven questions via a Zoom poll so that the study team could obtain a baseline reading of their perspectives on key issues covered in the working group meeting. The poll was repeated on the second day to observe if members' opinions shifted as a consequence of the meeting. A comparison of the *pre* and *post* results can be found attached as Appendix D.

The working group was asked whether they agreed or disagreed with the following statements:

1) DTC microbiome-based tests currently on the market have benefit to consumers.
2) DTC microbiome-based tests currently on the market have benefit to physicians.

3) DTC Gut microbiome-based tests can indicate what kind of diet is optimal for a consumer.
4) DTC Gut microbiome-based tests can indicate that a probiotic is indicated for a consumer.
5) Probiotics can be custom-tailored based on gut microbiome-based test results to improve a consumer's/patient's gut health.
6) The primary risk to consumers who order DTC microbiome-based tests is out-of-pocket cost.
7) There is reason to be concerned about how DTC microbiome-based testing companies use customer data.
8) There is reason to be concerned about privacy of data generated by DTC microbiome-based tests.
9) These tests should not be made available to patients/consumers without authorization of a physician.
10) These tests should not be regulated.
11) These tests require some regulation of the quality/validity of test results.

7. DTC Genetic Testing as a Model

For the last presentation of the first day of the meeting and just prior to Breakout Session #2, **Dr. Toni Pollin, Professor, University of Maryland School of Medicine**, discussed DTC *genetic* testing and addressed (1) the state of the science, (2) the industry, and (3) knowledge gaps.

There are many DTC genetic tests[2] and consumer-initiated genetic tests[3] on the market that test for a variety of applications. For example, 23andMe markets Wellness reports of a consumer's genetic predisposition for caffeine consumption, deep sleep, weight, lactose intolerance, etc., and Trait reports of a consumer's genes for bitter taste perception, cheek dimples, cleft chin, etc. In a 2017 promotion, another company, Orig3n, planned to offer DNA test kits to Baltimore Ravens fans to predict the level of their athletic performance but concerns over informed consent and privacy prevented the giveaway.[4]

The DTC genetic testing field is crowded with companies claiming to detect the genetic risk of disease by identifying certain genetic variants associated with disease. Companies began marketing genetic risk tests in 2007 with the claim that they could detect the risk of type 2 diabetes and thereby help consumers prevent diabetes with a healthy lifestyle. There were concerns, however, over false negatives when a genetic variant associated with a disease is not tested and issues with clinical validity if the same variant is used to predict different diseases. Further, there were concerns about the clinical utility of these tests because it was unclear how useful they were to predict disease.

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[2] Genetic testing that is ordered by a consumer without the required involvement of a doctor.
[3] Genetic testing that is requested by a consumer and must undergo review by a lab-contracted doctor to order the test.
[4] In addition, Maryland law prohibited the testing. This law was subsequently changed in 2019 but still prevents DTC testing in the state. Sarah Beth S. Kuyers & Karen Lovitch, *Maryland Legislature Passes Bill Allowing Direct Advertising of Certain Laboratory Tests*, MINTZ (Apr. 15, 2019), https://www.jdsupra.com/legalnews/maryland-legislature-passes-bill-38676/.

FDA ultimately shut down these genetic risk tests after determining that they were medical devices that needed regulatory approval. 23andMe then worked with FDA to obtain approval for carrier screening tests that identify an individual's genetic predisposition (i.e., risk) for certain diseases or conditions.[5] In accordance with its FDA approval,[6] 23andMe must disclose that not all possible variants of a disease are tested, but it is unclear whether consumers truly understand what this means. Also, the list of tested conditions has expanded, and it is unclear which of these new conditions are FDA approved.[7] Perhaps FDA does not object to the expanding list of conditions because the test is marketed as low-risk for a healthy lifestyle and is not diagnostic or therapeutic.[8] Finally, the clinical validity of the 23andMe carrier screening tests is questionable because false positives have been found in the raw data.

All of this begs the following regulatory questions: (1) is current regulation of DTC genetic testing adequate and appropriate; (2) are DTC genetic tests compliant with regulations; (3) are disclaimers enough; and (4) what are the risks of these products? Dr. Pollin's PowerPoint presentation may be found **here**.

8. Breakout Session #2

In this breakout session, Similarities and Differences between Microbiome-Based Tests and Genetic Tests, working group members were asked the following questions:

1) What similarities and differences do you see between DTC microbiome-based tests and DTC genetic tests? In thinking about your answers consider the following:
   a. What is being looked at in each?
   b. What are the risks and benefits of each and the magnitudes of those risks and benefits?
   c. What is the state of the science of each?
   d. Are there differences in the quality of the analysis and test results?
   e. What information can each reveal about us?
   f. What type of recommendations are provided by each testing service?
   g. Is the business model the same or different?
   h. Are incidental findings an issue for DTC microbiome-based tests?
   i. Are there familial implications for DTC microbiome-based tests?

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[5] FDA allowed marketing of the 23andMe Personal Genome Service Genetic Health Risk (GHR) test to inform consumers about their genetic risk of developing ten genetic diseases or conditions. U.S. FOOD & DRUG ADMIN., *FDA allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions* (Mar. 28, 2018), https://www.fda.gov/news-events/press-announcements/fda-allows-marketing-first-direct-consumer-tests-provide-genetic-risk-information-certain-conditions.

[6] FDA's approval was based on its review of data from 23andMe under the "de novo premarket review pathway, a regulatory pathway for novel, low-to-moderate-risk devices that are not substantially equivalent to an already legally marketed device." *Id.*

[7] With its decision to allow marketing of the 23andMe GHR test, FDA determined that future, similar GHR tests would be exempt from premarket submission after a company submitted its first premarket notification. *Id.*

[8] The 21st Century Cures Act does not require premarket testing for low risk tests. 21 U.S.C. § 355(i)(4) (2016).

The most commonly cited difference between microbiome-based tests and genetic tests was that genetics does not change but the microbiome may change over time in response to a variety of influences. Another difference is that genetic testing is far ahead of microbiome-based testing, and, consequently, genetic tests are better validated and more clinically actionable than microbiome-based tests.

Also, some working group members raised the point that the cultural narrative of having certain "genes" includes a sense of identity that is inherent to who you are (e.g., Am I really African-American, or really white?). This is generally not the case for having certain microorganisms, but there is a growing cultural narrative about "good bacteria" and having a "natural" body on the microbiome side. Further, unlike microbiome data, genetic data has been sought by law enforcement in order to identify potential suspects in criminal cases directly or through family members; although there are some familial implications with the microbiome, there are fewer than for genetics.

The most commonly cited similarity between these two tests was that both test results have been "hyped" as being a gateway to personalized medicine when that has proved to be an over-simplification and over-selling of how these test results can be used. Further, the companies selling these tests have similar business models in that they both make health claims in their marketing, i.e., connect the presence or absence of the target genetic or microbial variant with certain health states.

The Second Day

9. Regulatory Scope & Overview

On the second day of the meeting, **Diane Hoffmann, Director of the Law and Health Care Program, University of Maryland Francis King Carey School of Law and PI on the project**, briefly reviewed the results of Breakout Sessions #1 and #2 from the first day and then presented a list of regulatory possibilities for DTC microbiome-based tests.

Options for federal regulatory oversight of these tests include:

1) CMS regulation under the CLIA statute (e.g., testing lab certification and oversight of testing quality)
2) FDA regulation under the Food, Drug, & Cosmetic Act (FDCA) (e.g., regulation of medical devices, software, and marketing claims)
3) Federal Trade Commission (FTC) regulation (e.g., regulation of advertising)
4) HHS, Office for Civil Rights regulation under HIPAA (e.g., oversight of data privacy)
5) HHS, NIH (e.g., human subjects research protections)
6) Equal Employment Opportunity Commission under the Genetic Information Nondiscrimination Act (GINA) (e.g., prohibition against using data for employment or insurance that may be harmful to the tested individual)
7) CMS regulation (e.g., insurance coverage & fraud)

Other regulatory options include (1) state laws (e.g., consumer protection; prohibitions on DTC genetic testing; state GINA laws; and malpractice/product liability); (2) constitutional protections (e.g., search & seizure under the Fourth Amendment and free speech under the First

Amendment); and (3) soft law (e.g., laboratory accreditation, professional guidelines, and industry standards).

Hoffmann stated that the focus of this first working group meeting is the background science, testing quality, and regulation of testing labs under CLIA. The second working group meeting will focus on FDA regulation under the FDCA and FTC regulation, and the third working group meeting will focus on regulation of data privacy, use of data and protection from discrimination, and, possibly, insurance coverage/fraud. Diane Hoffmann's PowerPoint presentation may be found **here**.

10. Determining Test Quality

The next two presentations focused on test quality terminology and test analytic steps, respectively. These presentations immediately preceded Breakout Session #3.

Dr. Mary-Claire Roghmann, Professor, University of Maryland School of Medicine, defined and discussed the testing terms (1) analytic validity, (2) clinical validity, and (3) clinical utility. After a diagnostic sample is collected and prepared, it is analyzed, the results are reported, the results are interpreted, and clinical action is taken. Analytic validity asks if the sample was accurately analyzed, i.e., does the test accurately measure the analyte/substance of interest. Clinical validity asks whether measuring the analyte in the sample accurately detects individuals with a specific condition. Clinical utility asks whether positive results lead to treatment or other intervention that improves health outcomes.

The focus of analytic validity is whether a test is sensitive and specific with respect to detecting the analyte in the sample. Test sensitivity measures the smallest quantity of an analyte that can be reproducibly distinguished from background levels in a given assay system. This is also known as the limit of detection. Test specificity assesses the ability of an analytical method to detect only the analyte that it was designed to measure.

The focus of clinical validity is whether a test is sensitive and specific with respect to detecting individuals with a specific disease, i.e., does a positive test mean that the tested individual definitely has the disease (i.e., sensitivity), and does a negative test mean that the tested individual definitely does not have the disease (i.e., specificity). The highest sensitivity (i.e., the test detects all true positives) is desired when a disease is serious and treatable, or when false-positive results will not lead to serious clinical or economic problems. The highest specificity (i.e., the test detects all true negatives) is desired when disease absence has either psychological or public health value, or when false-positive results might cause serious clinical or economic problems.

The focus of clinical utility is not whether a test is sensitive or specific but whether a test result leads to clinical action (i.e., is there a treatment or intervention that will benefit the patient). Other considerations of clinical utility include: are there risks that may result from using the test, and is there value in using the test even when no clinical intervention is available? Dr. Roghmann's PowerPoint presentation may be found **here**.

Dr. Daniel McDonald, Scientific Director, American Gut Project, University of California San Diego School of Medicine, presented on the analytic steps in gut microbiome analysis. Although the commercial microbiome-based testing market focuses on individual samples, accurately characterizing the human microbiome depends on the careful collection and analysis

of multiple samples at the population level. Differences in how samples are collected and prepared, and different analytic techniques can impact the accuracy of a sample analysis.[9]

For example, how a sample is shipped and preserved can affect the health of the organisms and, consequently, the microbial composition of the sample. Similarly, buffers added to the sample, contaminated reagents, and inadvertently mixing samples can affect the microbial composition of the sample. Given the variety of collection and preparation methods available and their possible impacts on sample analysis, the sample collection and preparation analytic step needs to be well standardized.

Regarding analytic techniques, microbial taxonomic analysis using 16S rRNA amplicon sequencing is one good way of identifying microbes because the 16S ribosome is fairly resistant to evolutionary pressures, i.e., does not change with each subsequent bacterial generation. 16S rRNA analysis, however, has poor resolution and is not reliable for microbe identification below the genus level. Shotgun sequencing is another way of identifying microbes because it sequences all of the DNA in a sample and aligns short sequences of the DNA to a reference database. Identification of microbes from an abundance of DNA in a sample depends on having a comprehensive database against which the DNA can be compared. Currently, however, reference databases for the human microbiome are far from complete.

The Microbiome Quality Control (MBQC) project is a collaborative effort to standardize microbiome sample collection methods, techniques and protocols for handling microbiome samples, and microbiome analytic techniques.[10] However, the project needs more funding and additional work to be able to generate guidelines for the microbiome field.

An example of a sequencing workflow tool is QIIME2 for amplicon (e.g., 16S rRNA) sequencing. QIIME2 performs quality control over input sequencing, it clusters sequences into operational taxonomic units (OTUs), and it taxonomically annotates sequences by looking for similar sequences in a reference database. The main output of the QIIME2 workflow is a feature table that describes the abundance of each OTU in a sample. QIIME2 tools also include alpha diversity (e.g., total taxa from each microbial community present in a sample), beta diversity (e.g., summary of multiple microbial communities and how each community relates to another), and principal coordinates analysis (PCoA) which allows these relationships to be visualized.

Accurate characterization of microbiome populations is challenged by a taxonomy that does not necessarily reflect microbial evolution. Microbes were originally grouped based on their morphology and metabolic activity and not based on their genetics; consequently, some distantly related organisms were inaccurately grouped into one taxa. For example, *Clostridium* spp. include organisms that inhabit the soil and organisms that live in the gastrointestinal tract. Also,

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[9] *See e.g.*, Ana Yun, Bill Mohn, Karl Moran, & Pedro Dimitriu, *How to Plan and Conduct a Microbiome Study*, MICROBIOME INSIGHTS (last visited Aug. 1, 2021), https://drive.google.com/file/d/1ke-jx8t0_gTukvemjdQ-sDgNWYlrPD0l/view.

[10] For more information about the MBQC, *see* Rashmi Sinha et al., *The microbiome quality control project: baseline study design and future directions*, 16 GENOME BIOL. 276 (2015), https://genomebiology.biomedcentral.com/track/pdf/10.1186/s13059-015-0841-8.pdf.

microbes are differentially abundant across the gut, so a single sample may not represent the true microbial composition of the gut. In spite of these challenges and although microbiome reference databases are incomplete, microbiome research has uncovered a few truisms. For instance, longitudinal sampling of the same person reveals a relatively unchanging microbiome, and, when people live close together, a portion of their microbiomes overlap. Dr. McDonald's PowerPoint presentation may be found **here**.

11. Breakout Session #3

In this breakout session, Analytic Steps and Parameters of Quality, working group members were asked the following questions:

1) Are the analytic steps and parameters of quality the same for microbiome tests as for genetic tests? In thinking about your answers, consider the following:
   a. What are challenges for establishing analytical validity in the microbiome context (as compared to genomic)? Is there an analog for "variant" in the microbiome context?
   b. What are the challenges to establishing clinical validity in the microbiome context (as compared to the genomic)?
   c. Do outcomes of a microbiome-based analysis map on to the same continuum as genetic test results? i.e., "geneticists classify variants into one of five categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign." (Evans, et al.[11]) What would be outcomes for microbiome-based tests?
   d. Is there the potential for a microbiome-based risk score (similar to a genetic risk score)?
   e. Does the concept of "penetrance" have an analog in the microbiome context?

Working group members observed that the analytical validity of microbiome-based tests could not be adequately assessed without knowing the testing methodology used by the laboratory. The group also noted that the issue of analytical validity encompasses the entire testing ecosystem from sample collection and transport to data generation techniques and analytical algorithms. According to the group, challenges in establishing clinical validity include: **(1) difficulty in establishing a control that represents "normal" in the population; (2) lack of standardization or established reference ranges in the microbiome field; and (3) lack of knowledge regarding what constitutes a healthy microbiome**.

12. Regulating Test Quality

The final presentation of the meeting was delivered by **Dr. Barbara Evans, Professor of Law and Engineering, University of Florida Levin College of Law & Wertheim College of Engineering.** Dr. Evans gave an overview of how CLIA works and described what CLIA does/does not regulate. She began by explaining that *in vitro* diagnostic (IVD) products are "test kits" made by a device manufacturer and regulated by FDA. In contrast, laboratory-developed

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[11] Barbara J. Evans, et al., "How Can Law and Policy Advance Quality in Genomic Analysis and Interpretation for Clinical Care?" 48 J. Law, Med. & Ethics 44, 48 (2020).

tests (LDTs), which are the type of tests we are discussing, are made by labs for their own use in testing patients and are regulated by CMS under CLIA. Although FDA claims that it can regulate LDTs, it has exercised enforcement discretion over these tests and has not regulated them.

CLIA regulates freestanding labs and clinical labs that examine biospecimens "for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."[12] The CLIA statute does not define "diagnosis, prevention, or treatment" and looks to state law to supply these definitions. Also, unlike FDA which regulates tests differently if they are for "wellness" as opposed to "diagnosis," this distinction is not binding on CMS for the purpose of determining the reach of CLIA jurisdiction; here again, CLIA looks to state law.

Under the CLIA statute, FDA is responsible for determining whether a given type of testing counts as "high complexity," "moderate complexity" or "low complexity," and CLIA issues different types of certification based on this determination. For example, the following types of CLIA certification apply to high complexity tests: registration, compliance, and accreditation. Microbiome-based tests would be considered high complexity tests.[13]

A CLIA certificate of registration temporarily allows a lab to continue high complexity testing until it acquires a certificate of compliance or accreditation. A certificate of compliance applies when the CLIA statute sets the regulatory standard for the testing lab and the inspection is done by a state inspection body. A certificate of accreditation applies when a testing lab elects to use the standards and inspection developed by a private accreditation body such as the College of American Pathologists (CAP) or the Joint Commission. CAP is particularly knowledgeable about genome-based standards, and, for this reason, may be a preferred way of achieving CLIA compliance for microbiome-based testing labs.

There are multiple regulatory pathways overseen by different agencies to get a product to market, and which pathway a company chooses is mostly a business decision. When a microbiome-based company makes an analytic claim about its test (i.e., the test accurately identifies a microbe), FDA under FDCA and CMS under CLIA share jurisdictional oversight of the claim. CLIA jurisdiction does not extend beyond analytic claims, however, and only FDA can demand to see the data that supports a claim of clinical validity. FDA has oversight of a clinical utility claim (e.g., an "intended use" claim), but, if the product is used in the clinic, practice and clinical use standards (e.g., practice of medicine and medical malpractice) apply. For microbiome-based tests that are not used in the clinic, clinical utility oversight from a trade group or professional society that sets recommended clinical standards, e.g., the American Gastroenterological Association, may serve as a type of self-regulation.

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[12] 42 U.S.C. § 263a(a) (2020).

[13] FDA classifies genetic tests as moderate or high complexity but requires genetic testing labs to meet the criteria for high complexity tests. Microbiome-based tests use genetic analysis and would likely be considered high complexity tests by FDA. Note that a CLIA certificate of waiver does not apply to high complexity tests and, therefore, would not apply to microbiome-based tests. *See* U.S. DEP'T HEALTH & HUM. SERVS., *The CLIA Framework*, NAT'L HUM. GENOME RES. INST. (last visited Jan. 18, 2021), https://www.genome.gov/Pages/PolicyEthics/GeneticTesting/The_CLIA_Framework.pdf.

Microbiome-based tests rely on software for analysis, but there is an ongoing question about how such 'omics testing software should be regulated. CMS does not have the resources under the CLIA statute to take on the regulation of this software, and FDA suggests that it can regulate the software used in 'omics testing. The agency says it has this authority even when the test, itself, is a lab-developed test that FDA may not have authority to regulate. FDA's oversight of this type of software could have unintended consequences in the form of new types of liability (e.g., product liability) for labs and third-party providers of software. Dr. Evan's PowerPoint presentation may be found **here**.

13. Breakout Session #4

During this breakout session, CLIA Regulation, working group members were asked the following questions:

1) Should microbiome-based testing companies be subject to CLIA certification? i.e., do they come within the covered entities listed below?
   a. CLIA applies to all laboratories that examine "materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" (42 CFR § 493.2).
2) Are there shortcomings of CLIA that do not adequately regulate the analytical validity of microbiome based tests? What are they? Should there be some standardization of testing? (valid v. invalid methods) In answering this question you may want to consider the following from the article by Evans et al.[14]
   a. "CLIA does not include an external review component (either before or after a laboratory begins to offer a test) to evaluate a laboratory's evidentiary basis for performing a test or for the interpretive conclusions included in the test report."
   b. "CLIA [] does not specifically regulate . . . the software algorithms used to generate and interpret genomic sequence data." (But companies must validate that the software does what it's intended to do.)
   c. "CMS has not defined specific educational or training requirements for bioinformatics personnel even though that discipline requires different expertise than other aspects of laboratory testing."
   d. "CMS has not specified requirements for software validation. Furthermore, when the interpretive bioinformatics is performed by an entity separate from the laboratory that generated the sequencing data (i.e., the increasing use of a separate 'dry lab' or 'unbundled' interpretation services), CLIA arguably does not apply to that separate entity."
   e. "[T]here is no external, data-driven regulatory review of clinical validity before a laboratory offers a new test."
3) Are challenges for genomic testing oversight by CLIA similar for microbiome-based testing, e.g., "genomic test results can include a significant amount of information for

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[14] Evans, *supra* note 11, at 44–68.

which the laboratory cannot provide 'pertinent information required for interpretation' and for which the laboratory will not be able to assist clients in interpreting test results;" is this the same for microbiome-based tests? Are there alternatives to federal regulation including "soft law" options for "regulating" microbiome-based testing companies that we should consider? State regulation? Model State law? Professional Association recommended standards, e.g., CAP (College of American Pathologists) inspection?

Working group members generally agreed that CLIA regulation of microbiome-based testing labs is a minimum requirement regardless of the claims made by the company. The issues for the group, then, were what kind of CLIA regulation is needed and to what extent. For instance, CLIA requires you to meet a quality standard, but it does not require using the best tests available.

Several working group members questioned what CLIA would actually regulate given that there is no standard for analytical validity in microbiome-based tests. Some of these members commented, however, that NIST (a government agency that develops standards) made mock communities of bacteria in an effort to characterize the microbiome (note that this is still a work in progress).[15] One working group member suggested that CLIA should govern compliance but not necessarily set the standards; rather a separate body should offer accreditation to allow for standards to evolve over time (e.g., accreditation by CAP, followed by CLIA certification).

In contrast to CLIA, the working group noted that FDA may not be ready to regulate these tests because FDA oversight would impede innovation in the microbiome field. A few working group members felt that microbiome-based tests should be regulated by a mix of CLIA and state regulation and, if someone is harmed, through private legal action. Several in the group also advocated for microbiome industry self-regulation (e.g., standardization) because government oversight tends to result from unresolved problems in an industry.

14. Polling Questions – Second Day

Working group members answered a series of questions via Zoom polling about the analytical and clinical validity of DTC microbiome-based tests.

   A. Regulatory oversight of analytical validity.

A majority of the working group believed that some or all of microbiome-based tests are analytically valid, however, a stronger majority felt that the analytical validity of these tests can be improved. While the majority agreed that microbiome-based tests should be performed in CLIA-certified labs, the majority also believed that there are regulatory alternatives to CLIA that should be applied to these labs. Below are the group's responses to the questions posed on analytical validity.

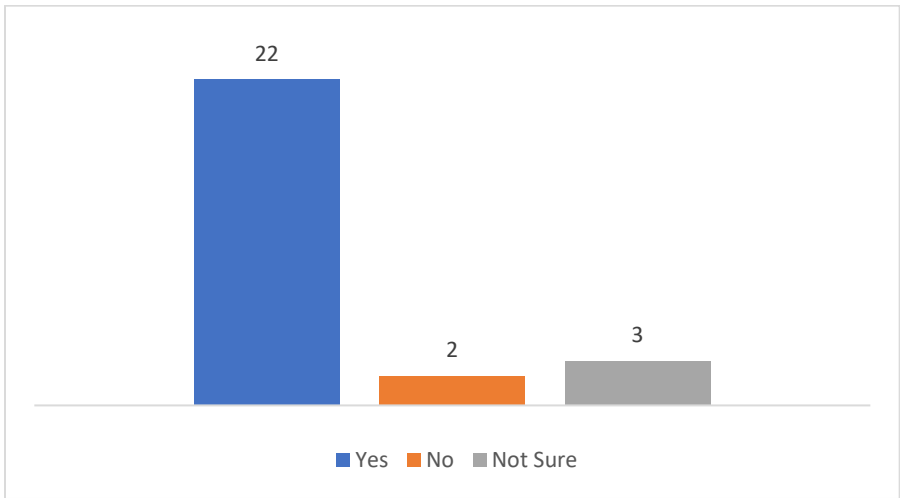   (1) Do you think the current DTC microbiome-based tests are analytically valid?

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[15] NAT'L INST. STDS. & TECH., *Microbial Measurements* (updated July 9, 2020), https://www.nist.gov/mml/bbd/core-capabilities/microbial-measurements.
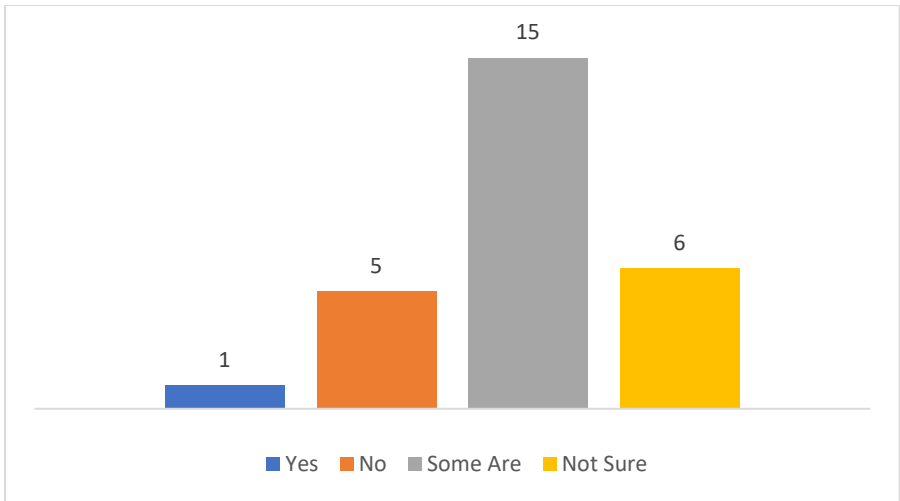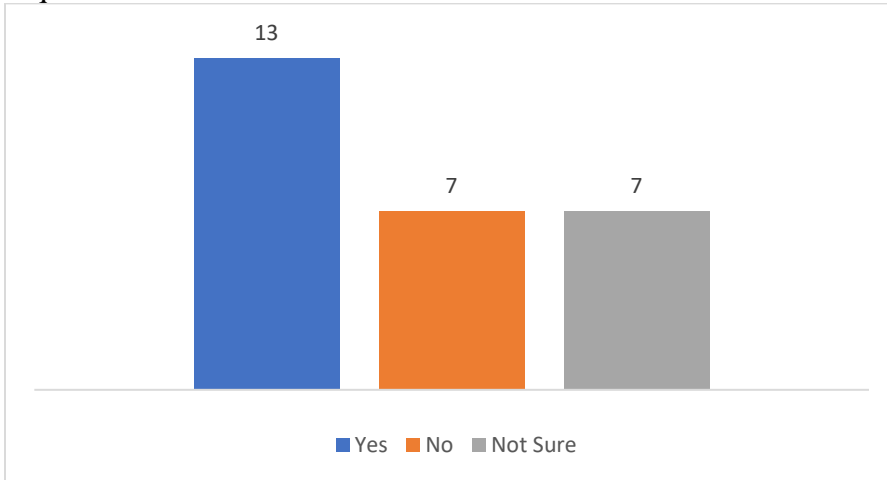
(2) Could the analytical validity of these tests be improved?
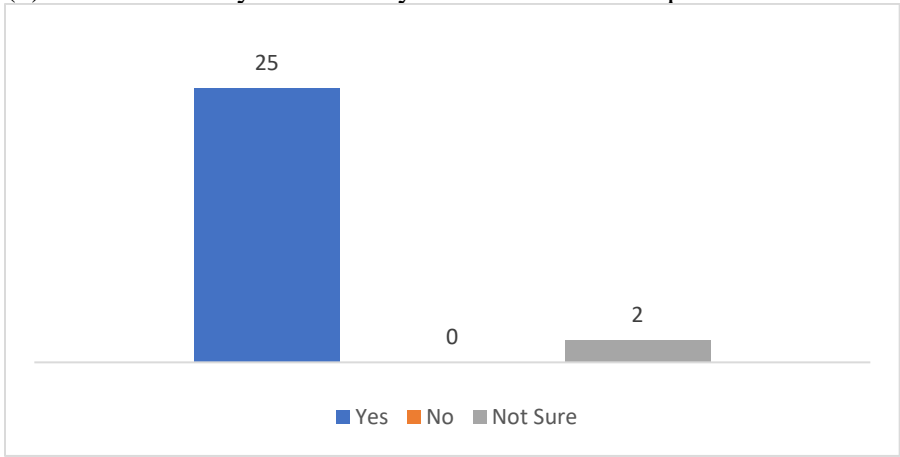
(3) Do you believe DTC microbiome-based testing should be performed in a CLIA certified lab?

(4) Should CLIA regulate the software algorithms used to generate and interpret genomic sequence data?

(5) Should CLIA require specific educational or training requirements for bioinformatics personnel working at DTC microbiome-based testing companies?
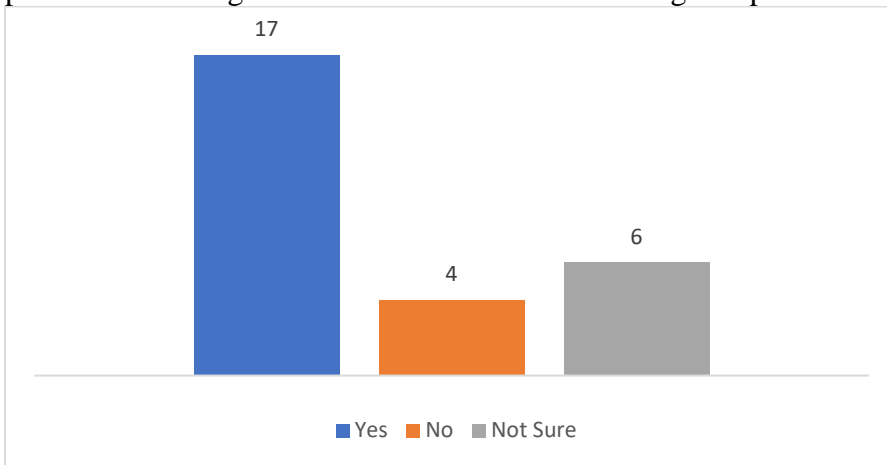

(6) Are there alternatives to CLIA standards that should be applied to DTC microbiome - based testing labs? E.g., state regulation, professional association standards? Industry association standards?

21 | 0 | 6
Yes | No | Not Sure
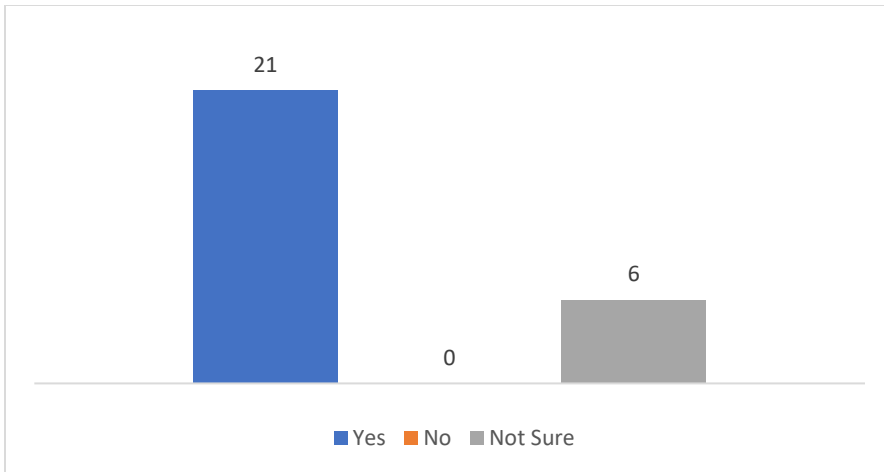
B. Regulatory oversight of clinical validity.

A majority of the working group felt that these tests are not clinically valid, and that labs should undergo an external review of the evidentiary basis of their tests before they can make interpretive conclusions about the results. The group was split, however, about whether the clinical validity of microbiome-based tests should be regulated at this time. Below are the group's responses to the questions posed on clinical validity.

(1) Do you think the current DTC microbiome-based tests are clinically valid?

0 | 16 | 6 | 5
Yes | No | Some Are | Not Sure
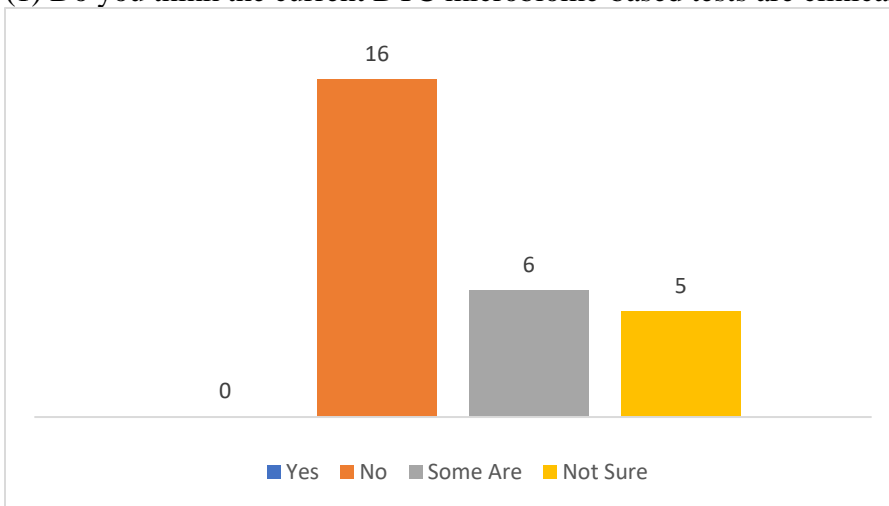
(2) Do you think regulators should require an external review component (either before or after a laboratory begins to offer a test) to evaluate a microbiome-based testing laboratory's evidentiary basis for performing a test or for the interpretive conclusions included in the test report?

Yes · No · Not Sure
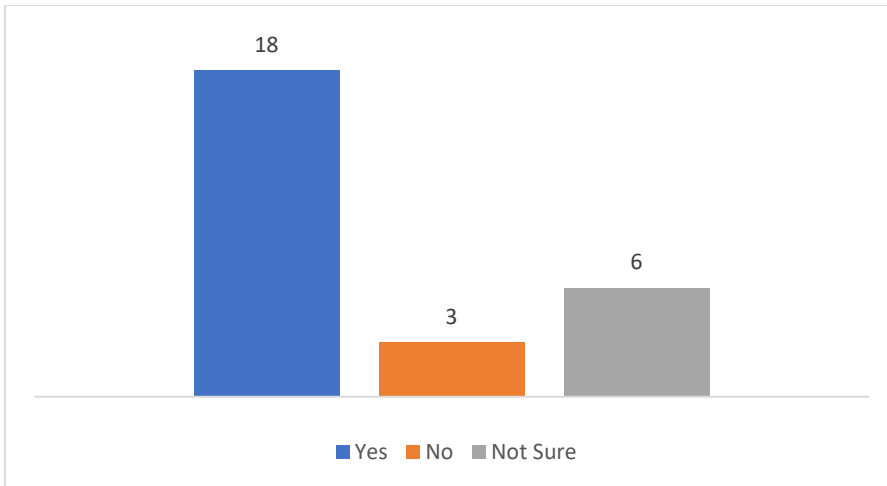
(3) Is it premature to regulate clinical validity of these tests at this time?

Yes · No · Not Sure
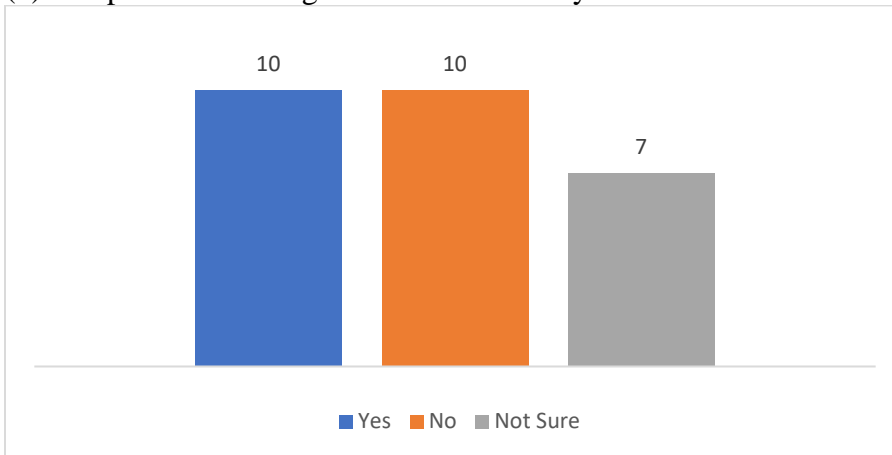
Working group members also repeated the eleven polling questions from the first day of the meeting to assess their attitudes about DTC microbiome-based tests. A comparison of the *pre* and *post* results is provided in Appendix D.

Appendix A – Working Group Members

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[1] Mr. Manoj Dadlani serves as Chief Executive Officer at CosmosID, Inc., a genomic big data company focused on rapid identification of microorganisms for infectious disease diagnostics, public health surveillance, food safety monitoring, pharmaceutical discovery, and microbiome analysis for health and wellness. CosmosID has built the largest curated databases for best-in-class microbial identification and characterization. So far, the technology has already been utilized in over a dozen high impact peer reviewed publications. Previously, Mr. Dadlani served as a partner at Applied Value Group, a management consulting and investment firm, and was co-founder and Chief Executive Officer at Rasa Industries, Ltd., a leading beverage manufacturing company in northern Nigeria. Mr. Dadlani has substantial experience in strategy, M&A, supply chain management, product development, marketing and business development. Mr. Dadlani received his Bachelor's and Master's degrees in Biological Engineering from Cornell University.

[2] Dr. Tharak Rao is a U.S. trained physician with expertise in internal medicine, rheumatology, and drug and diagnostic test development. Prior to being named Chief Medical Officer at Mobility Bio, Inc. of Palo Alto, CA, Dr. Rao was Senior Vice President at Assembly Biosciences, South San Francisco, CA, where he led clinical development for the company's microbiome platform and, prior to that, Chief Medical Officer at Prometheus Labs, San Diego, CA. His earlier career included roles of increasing responsibility at Novartis and Genentech. Dr Rao completed his internal medicine residency training at UT-Houston and a rheumatology fellowship at the University of Michigan.

[3] Ms. Pita Navarro is the Head of Clinical Ops & Research at Evvy, where her mission is to take the guesswork out of women's health. For the past 4 years, she was on the founding team at Athelas, a biotech company deploying computer vision technology to monitor key blood metrics for chronically ill patients. At Athelas, she led all clinical validation in psychiatry & oncology, proving their technology led to better patient outcomes. She was a key team member in implementing and distributing Athelas products throughout the healthcare system.

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[4] Dr. McDonald is the Scientific Director for The Microsetta Initiative and the American Gut Project, run by the School of Medicine at UC San Diego. His research focuses on the complex microbial communities associated with humans, with the environment, and how to scale microbiome analysis to large sample sizes. He has played central roles in the development of highly cited analysis tools, such as QIIME, Qiita, and PICRUSt, a Genomic Standards Consortium file format called BIOM, and Greengenes, one of the main microbial taxonomies used in the field. Dr. McDonald received a BS and PhD in Computer Science from the University of Colorado at Boulder under Prof. Rob Knight.

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[5] Mr. Cleland joined the Federal Trade Commission's Division of Advertising Practices in 1991. In 1996, Mr. Cleland was appointed Assistant to the Director of the Bureau of Consumer Protection and, in 1998, he was appointed Assistant Director of the Division of Service Industry Practices. He currently serves as Assistant Director of the Division of Advertising Practices. His primary area of expertise is the advertising and marketing of health-related products and services. He also supervises many of the Commission's health fraud law enforcement initiatives. Mr. Cleland supervised the FTC's review of the Endorsement and Testimonial Guides and the revision of the FTC's guidance on making effective disclosures on the Internet and other digital platforms (.com Disclosures). Mr. Cleland's most recent work has focused on supervising the Commission's efforts to stop sellers of bogus products/services promoted to treat or prevent COVID-19.

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[6] Dr. Langel is a recent graduate of the University if Maryland Law School where she specialized in health care law and cyber law. In addition to her law degree, she has a Ph.D. in molecular biology with a concentration in immunology. Dr. Langel retired from the U.S. Army at the rank of lieutenant colonel.

Appendix B

<p align="center">**Agenda for Microbiome Testing Working Group Meeting**
June 16-17, 2021</p>

<p align="center">**DAY ONE**</p>

10:00 – 10:15 (all times are ET)

    I.   **Welcome/Background/Purpose of Working Group – Diane Hoffmann, JD, MS, University of Maryland School of Law**

10:15 – 10:45

    II.   **Introductions**

10:45 – 12:15

    III.   **State of the Science**
- **a.** What do we know? Focus on Gut and Vaginal Microbiome
    - i. Is there a Core/Healthy Microbiome?
    - ii. Relationship between microbiome and health/disease
    - iii. Diagnostic potential; Predictive potential? What will the future bring?
    - iv. Knowledge Gaps
        1. **Speakers:**
            a. **Alex Khoruts, MD, University of Minnesota (gut) (10:45 – 11:15)**
            b. **Jacques Ravel, PhD, University of Maryland (vaginal) (11:15 – 11:45)**
- **b.** What do we know about the relationship between the Microbiome and diet/nutrition and dietary supplements? Knowledge Gaps?
    1. **Speaker: Suzanne Devkota, PhD, Cedar-Sinai Medical Center (11:45 – 12:15)**

12:15 – 12:50

    IV.   **Industry Initiatives**
- **a. Speakers: Christopher Mason, PhD (Cornell Medicine/Onegevity) & Eran Elinav, MD, PhD (Weizmann Institute/Day Two) (with Moderator)**

12:50 – 1:05

- **b. Review of Sample Patient Test Results – Erik von Rosenvinge, MD, University of Maryland School of Medicine**

1:05 – 1:50   **LUNCH BREAK**

1:50 – 2:30

  C. SMALL GROUP BREAKOUT SESSION – Questions for Discussion:
   1. What benefits do you think these tests can provide to patients/consumers?
   2. What are the risks to patients/consumers?
   3. What questions, if any, would you have about these test results if you received them?
   4. What concerns, if any, do you have (or would you have if you had ordered one of these tests) about the use of these tests?
   5. Do you think these tests should be available to patients without authorization from a physician? Why or why not?
   6. These tests are virtually unregulated by FDA or other government agencies. Do you think they should be more regulated than they are? Why or why not?

2:30 – 2:45

 V. Interview and Focus Group Results
  a. Presentation – Felicia Langel, PhD, JD, University of Maryland School of Law

2:45 – 2:55

  b. Polling Questions

2:55 – 3:05

 VI. Regulatory Areas: Scope & Overview – Diane Hoffmann, JD, MS, University of Maryland School of Law

3:05 – 3:30

 VII. DTC Genetic Testing as a Model
  a. DTC Genetic Testing – Toni Pollin, PhD, University of Maryland School of Medicine
   i. State of the science
   ii. Industry
   iii. Knowledge gaps

3:30 – 4:10

  b. SMALL GROUP BREAKOUT SESSION
   i. Similarities and Differences between Microbiome tests and Genetic tests – Things to consider:
    1. Risks and Benefits
    2. State of the Science
    3. What is being looked at?
    4. What information can each reveal about us?

<div align="right">5. Type of recommendations provided by testing services</div>

4:10 – 4:15   c. Submission of Small Group results and Polling

<div align="center">**DAY TWO**</div>

10:00 – 10:15

    I.   **Review of Day One Small Group Breakout Sessions – Diane Hoffmann, JD, MS**

10:15 – 10:30

    II.   **Determining Quality of Tests**
        a. Parameters of Quality – Mary-Claire Roghmann, MD, MS, University of Maryland School of Medicine
            i.   Analytical Validity
            ii. Clinical Validity
            iii. Clinical Utility

10:30 – 10:50

        b. Analytic Steps in Gut Microbiome Analysis – Daniel McDonald, PhD, Scientific Director, American Gut Project / The Microsetta Initiative

10:50 – 11:30

        c. SMALL GROUP BREAKOUT SESSION: Questions re: Analytic Steps and Parameters of Quality
            i. Are they the same for microbiome tests as for genetic tests? Questions to consider:
                1. What are challenges for analytical validity in the microbiome context (as compared to genomic)? Is there an analog for "variant" in the microbiome context?
                2. What are the challenges to clinical validity in the microbiome context (as compared to the genomic)? Do outcomes of analysis map on to same continuum as genetic test results? What would be outcomes for microbiome-based tests? Is there the potential for a microbiome-based risk score (similar to a genetic risk score)?
                    a. Does the concept of "penetrance" have an analog in the microbiome context?

11:30 – 12:00 BREAK

12:00 – 12:10

          d. Reporting of Small Group Results

12:10 – 12:30

    III.   **Regulating Quality of Tests**
          a. Regulation under CLIA – Barbara Evans, PhD, JD, LLM, University of Florida
             i. Overview of how CLIA works
            ii. What it does and does not regulate

12:30 – 1:10

          b. SMALL GROUP BREAKOUT SESSION – Questions
             i. Should microbiome-based testing companies be subject to CLIA?
            ii. Are there shortcomings of CLIA that do not capture analytical validity of microbiome-based tests? Should there be some standardization of testing?
           iii. Are challenges for genomic testing oversight by CLIA similar for microbiome-based testing?
           iv. Are there alternatives to federal regulations including "soft law" options for "regulating" microbiome-based testing companies that we should consider?

1:10 – 1:30

          a. Polling on Oversight re: Analytical Validity
          b. Polling on Oversight re: Clinical Validity

    IV.   **NEXT STEPS**

Appendix C – Focus Group and Interview Results

Focus groups consisted of gastroenterologists & infectious disease specialists (GI); pediatric gastroenterologists (Ped GI); obstetrician-gynecologists (OB-GYN); functional medicine providers (Functional Med); tested consumers; and untested consumers. Interviewees were physicians, consumers, and microbiome researchers, In the tables below, participant responses to the issue posed (e.g., Benefits of microbiome-based tests) appear in the first column, and an X attributes the response to a particular group.

1. Benefits of microbiome-based tests.

Participant Responses	GI	Ped GI	OB-GYN	Functional Med	Researcher	Tested Consumer	Untested Consumer
1. Patient access to personal health data.		X	X	X		X	X
2. Baseline assessment of microbiome; informs changes in care.						X	X
3. Using DTC tests as an educational tool.				X			
4. DTC tests for STI may be more feasible and less stigmatizing.			X				

1) Several physician groups recognized that patients are increasingly empowered to request and obtain access to their personal health data. Physicians across most groups viewed this as a benefit of direct-to-consumer microbiome-based tests. Most consumers also recognized the benefit of access to personal health data from these tests.

2) Both tested and untested consumers felt that test results could provide a baseline understanding of a patient's microbiome which can be reassessed over time and correlated to changes in treatment regimens or dietary modifications. Although tested consumers shared this sentiment in theory, in reality, the test results failed to clearly correlate their microbiome to their health condition.

3) Functional medicine physicians had the most experience with microbiome-based tests; they used them as a part of a comprehensive panel of tests. One functional medicine physician who uses the tests thought they had educational value stating, "I [] 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."

4) A few OB-GYNs expressed the benefits of a direct-to-consumer STI (sexually transmitted infection) test, which can be conducted in private, is feasible, and may be considered less stigmatizing than traditional STI testing performed in a doctor's office.

2. Risks of microbiome-based tests.

Participant Responses	GI	Ped GI	OB-GYN	Functional Med	Researcher	Tested Consumer	Untested Consumer
1. Test recommendations may worsen health outcomes.	X	X	X	X	X		
2. Test results may lead to harmful or unnecessary prescriptions.	X	X	X	X	X		
3. Test results may cause fear and anxiety for patients.		X	X				
4. Tests may affect trust between patient and provider.		X	X				
5. Tests may give inaccurate STI results; stigma associated with vaginal microbiome.			X		X		

1) All physicians and researchers were concerned that patients would use these tests to self-medicate and that these testing companies may recommend that a customer address a specific microorganism which may not have clinical relevance. Additionally, addressing specific microorganisms using therapeutics or elimination diets could be harmful and disrupt the complex, symbiotic nature of the microbiome, leading to worse health outcomes.

2) Physicians in all groups and researchers stated concerns about tests that were ordered by providers, particularly if the provider was not well-versed in microbiome research, leading to harmful or unnecessary prescriptions. Researchers added that, as long as physicians are familiar with the microbiome, they may be able to interpret the results beyond the company's recommendations. For researchers, the danger lies in physicians taking clinical action based on mere associations between organisms and disease.

3) Pediatric gastroenterologists and OB-GYNs expressed particular concern that, when the test recommendations do not consider the patient's history or they focus on specific microorganisms that are common and not clinically relevant, this may cause fear and anxiety for consumers.

4) Pediatric gastroenterologists and OB-GYNs also spoke about how these tests may erode the relationship between the patient/family and the provider, particularly when the patient/family places more trust in a glossy, professional-looking report than the more mundane recommendations of the provider. One OB-GYN stated, ". . . 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 . . . report [that] looks pretty neat and official."

5) The OB-GYN groups were concerned about the accuracy of these tests, given the little information they had about how the tests detect STIs. These physicians also discussed the potential harms to patients receiving false-negative results for STI tests. One researcher discussed the potential stigmatizing effects of characterizing the vaginal microbiome stating, "I think that there's a history of how women are judged and assessed, and I don't think we need another instance where people are gonna be labeled based upon a very limited amount of information and an incomplete understanding of the complexity. And yet we're gonna label them. And we're gonna decide that they're not okay. In any case tell them that they're inferior [in] some way. I mean especially women of color [who] often have a higher risk of STIs. This often leads people to conclude that the reason why there's a higher risk of STIs is because they're promiscuous."

3. **Physician/consumer questions about test results.**

Participant Responses	GI	Ped GI	OB-GYN	Functional Med	Researcher	Tested Consumer	Untested Consumer
1. Using stool samples for microbiome tests.	X			X			
2. Analytical validity and lab processes.	X	X	X	X	X		X
3. Clinical validity and predictive ability of results.	X	X	X	X	X		
4. Limited understanding of the microbiome.	X	X	X	X	X	X	

1) A few physicians in the gastroenterology and functional medicine groups 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.
2) Physicians across all groups also raised questions about the analytical validity of microbiome tests. They were concerned about a company's ability to conduct the test properly and whether its process was standardized. Physicians also questioned the reference ranges for these tests, how ranges were determined, and on which populations they were normed. Most untested consumers also questioned the accuracy of test results, standardization across tests, and quality control.
3) In terms of clinical validity, physicians across all groups and researchers questioned the degree to which microbiome tests can accurately identify or predict a risk of disease or other outcomes. Physicians in the gastroenterology and pediatric gastroenterology groups, suggested that companies manufacturing these tests should provide data on how they determine clinical validity.

4) Several physicians across all groups also 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. Physicians explained that, due to this limited understanding, it is not possible to use microbiome test results to guide treatment decisions. Relatedly, researchers wanted to see more evidence of test efficacy and utility arising from sufficient numbers of statistically validated peer-reviewed clinical studies. Several tested consumers also reported that their physicians would not be able to interpret the test results because they are unfamiliar with the field or because there remain too many unknowns.

4. **Concerns about privacy and the use of information from the test results.**

Participant Responses	GI	Ped GI	OB-GYN	Functional Med	Researcher	Tested Consumer	Untested Consumer
1. Privacy of test samples and data.	X	X	X	X		X	X
2. Concerns about privacy and data use may be more theoretical.		X	X			X	X
3. Selling microbiome data.	X		X		X		
4. Denying insurance coverage.	X					X	
5. Companies conducting research using consumer data.		X		X			

1) Regarding privacy, physicians across all groups questioned who has access to test results and asserted that DTC companies need to make their policies transparent for consumers so they can make informed decisions before proceeding with a test. A few tested and untested consumers also reported that they were concerned about privacy and how their data might be used by third parties.
2) On the other hand, several participants in the OB-GYN and pediatric gastroenterology groups noted that privacy concerns may not be an issue at the moment because the microbiome field is still being explored. Until the science has established a connection between the microbiome and disease progression, these providers believe that privacy concerns are hypothetical. Several tested and untested consumers were not overly concerned about data use and privacy issues because they assume that, as a society, our personal data is no longer private.
3) Some physicians in the gastroenterology and OB-GYN groups were concerned about microbiome companies selling consumer data to pharmaceutical companies and targeting consumers for advertisements. One researcher also remarked, "This is all a bunch of [crap]. It's like pseudoscience right now. You know, lots of companies have made a

fortune [] [selling] th[is] kinda stuff, but [] it's important to recognize what it is, which is a pseudoscience, trying to make doctors and patients believe that there's something valid."

4) Physicians in the gastroenterology group predicted that, as scientists become more knowledgeable of the correlation between the microbiome and disease, insurance companies may use microbiome data to deny or limit insurance coverage for patients. One tested consumer was similarly concerned that microbiome test results might be used to "get my insurance rates really high."

5) Several physicians in the pediatric gastroenterology and functional medicine groups discussed concerns about these companies collecting data including microbiome samples and demographic data for their own research. Although this may be the standard in the industry, physicians believed that this should be transparent to the consumer.

5. **Physician authorization required/not required to order these tests.**

Participant Responses	GI	Ped GI	OB-GYN	Functional Med	Researcher	Tested Consumer	Untested Consumer
1. Preference for tests to be accessible only by physician order.	X	X	X	X			
2. Preference for tests to be accessible without a physician order.						X	X
3. Interpreting results with provider.		X	X	X	X	X	X

1) Most physicians across all groups believed that, given the concerns of analytic validity, difficulty in interpreting the test results, and potential harm of test recommendations, tests should be accessible only by a physician order.

2) For consumers, most believed that the public should be able to purchase these tests directly and without a physician order. For tested consumers, direct-to-consumer access to microbiome-based tests was particularly important because many physicians would not recommend or order these tests for their patients.

3) Several physicians and researchers suggested that, in order to reduce confusion and avoid potentially harmful treatments, microbiome-based test results should be interpreted by a provider. Several untested consumers and a few tested consumers stated that, although they believed that the public should have the ability to purchase these tests, they were unsure of how to interpret the results and, therefore, it was important to seek physician guidance.

6. **Extent of regulation appropriate for these tests.**

Participant Responses	GI	Ped GI	OB-GYN	Functional Med	Researcher	Tested Consumer	Untested Consumer

	1	2	3	4	5	6	7
1. Regulation of patient health information.	X	X	X	X			X
2. Regulation to standardize tests.	X	X	X	X			X
3. Regulation of test recommendations and marketing claims.		X	X		X		
4. Regulation of positive STI results.			X				
5. Need to balance regulation and innovation.			X	X		X	
6. Regulation of these tests is a lower priority issue.		X			X	X	X

1) Physicians noted that something like HIPAA should apply to microbiome-based test results. One untested consumer stated, "I guess I'd be looking for something like. . . HIPAA . . . . I'd be looking for what kind of protection do I have [and] who could have access to [my data]."

2) Physicians across all groups suggested standardizing reference ranges and regulating the process of identifying and reporting microorganisms to help ensure the analytical validity of microbiome-based tests and increase confidence in the results. Most untested consumers felt that these tests should be regulated by the FDA. These participants trusted the FDA and would have more confidence in the quality and accuracy of the tests if they were approved by this agency.

3) Physicians in the pediatric gastroenterology and OB-GYN groups suggested regulating the recommendations that accompany test results. They suggested a disclaimer stating that consumers should consult their physician before implementing new treatments based on test recommendations. Researchers felt that companies are overselling their product and cannot back up their health claims and, if physicians prescribe pharmaceuticals based on this data, then regulation is warranted.

4) A few OB-GYNs wanted to see regulation of positive tests for STIs, particularly they wanted to know if they are reported in public health systems and if partner tracing is conducted.

5) Despite most participants believing that these tests need to be regulated in some way, a few physicians discussed the need to ensure that regulation does not stifle innovation. These physicians stated that, rather than enforcing regulation, companies should be transparent about their processes to provide physicians and consumers with enough information to make informed decisions about the test. One tested consumer also expressed that the regulation of these tests must not preclude innovation, particularly as the microbiome field is in its nascent stage.

6) For pediatric gastroenterologists, the regulation of microbiome-based tests was a lower priority than other regulatory issues. These physicians reported that the lack of regulation for supplements, holistic treatments, or known harmful substances was a greater concern compared to microbiome tests. Two researchers also suggested that these tests are ultimately harmless, and consumers consent to the microbiome-based testing company's privacy policy and terms of service; therefore, regulation is not required. A few consumers in both the tested and untested groups were not concerned about regulation of these tests because they were not viewed as potentially harmful compared to drugs or other medical treatments.
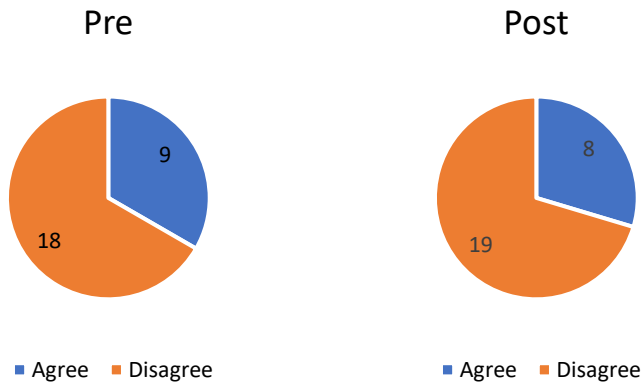
Appendix D – *Pre* and *Post* Polling – Attitudes about DTC Microbiome-Based Tests

Overall, working group members were skeptical about the value to consumers and providers of microbiome-based tests and doubtful of the claims made by DTC microbiome-based companies. Members were concerned about data privacy and how companies use consumer data and these concerns deepened by the end of the working group meeting. Members were split about whether the out-of-pocket cost of these tests is a significant risk to consumers but were unified in their belief that these tests require regulation. Finally, most members agreed that DTC microbiome-based tests should be available to consumers without provider authorization.
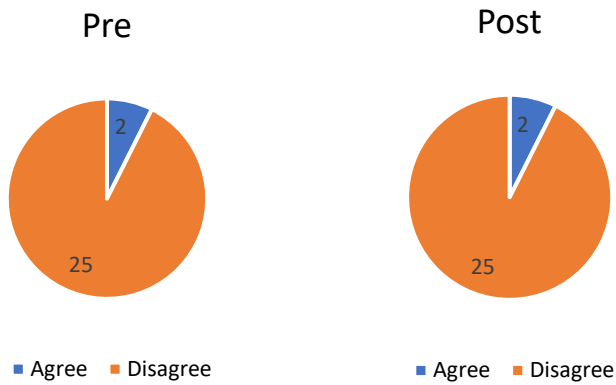
1. DTC microbiome-based tests currently on the market have benefit to consumers.
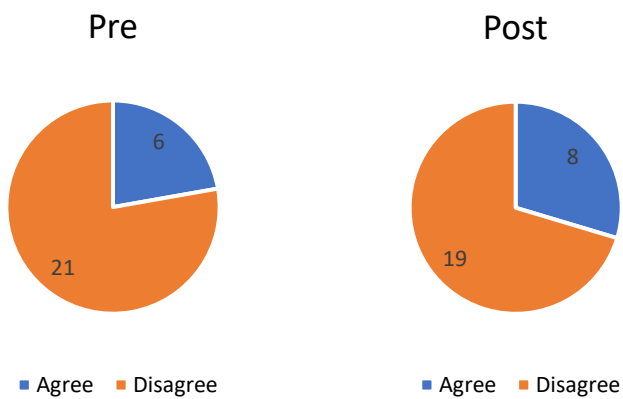

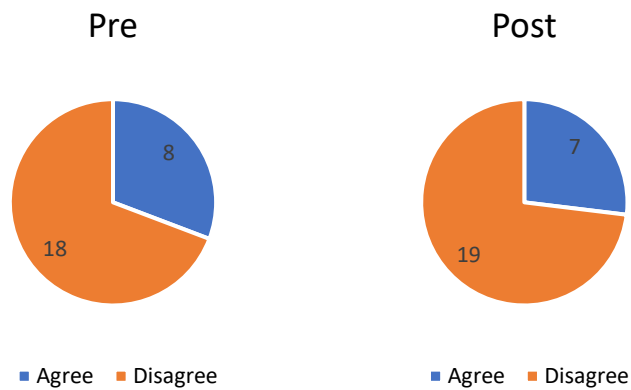2. DTC microbiome-based tests currently on the market have benefit to physicians.

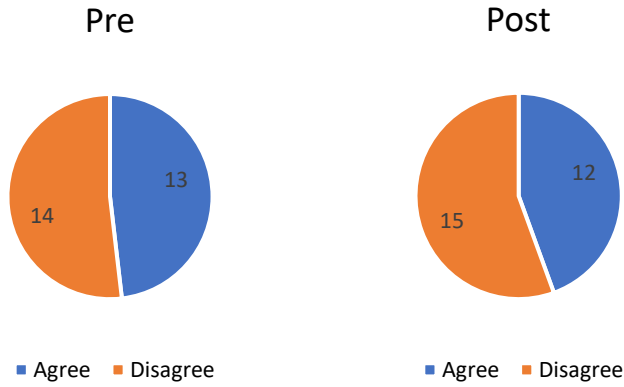3. DTC Gut microbiome-based tests can indicate what kind of diet is optimal for a consumer.

Pre   Post

Pre: Agree 2, Disagree 25 — Agree ■ Disagree

Post: Agree 2, Disagree 25 — Agree ■ Disagree

4. DTC Gut microbiome-based tests can indicate that a probiotic is indicated for a consumer.

Pre   Post

Pre: Agree 6, Disagree 21 — Agree ■ Disagree
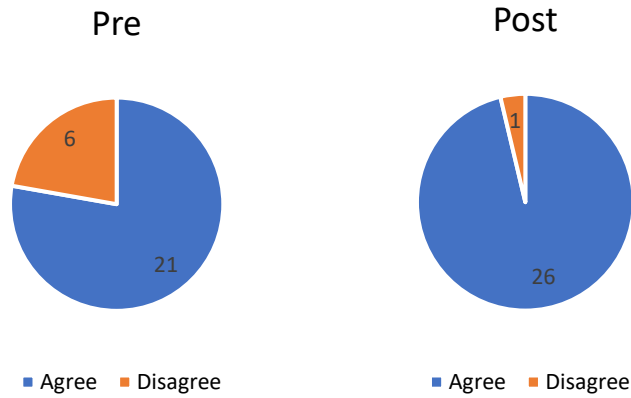
Post: Agree 8, Disagree 19 — Agree ■ Disagree

5. Probiotics can be custom-tailored based on gut microbiome-based test results to improve a consumer's/patient's gut health.
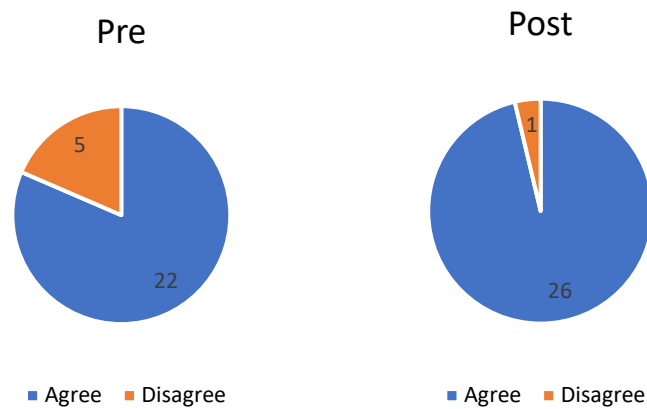

Pre   Post

Pre: Agree 8, Disagree 18 — Agree ■ Disagree

Post: Agree 7, Disagree 19 — Agree ■ Disagree

6. The primary risk to consumers who order DTC microbiome-based tests is out-of-pocket cost.

Pre

13

14

■ Agree ■ Disagree

Post

12

15

■ Agree ■ Disagree

7. There is reason to be concerned about how DTC microbiome-based testing companies use customer data.

Pre

6

21

■ Agree ■ Disagree

Post

1

26

■ Agree ■ Disagree

8. There is reason to be concerned about privacy of data generated by DTC microbiome-based tests.

Pre

5

22

■ Agree ■ Disagree

Post

1

26

■ Agree ■ Disagree

9. These tests should not be made available to patients/consumers without authorization of a physician.

Pre

Agree: 6
Disagree: 20

Agree ■ Disagree

Post

Agree: 6
Disagree: 20

Agree ■ Disagree

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10. These tests should not be regulated.

Pre

Agree: 4
Disagree: 23

Agree ■ Disagree

Post

Agree: 0
Disagree: 27

Agree ■ Disagree

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11. These tests require some regulation of the quality/validity of test results.

Pre

Agree: 26
Disagree: 1

Agree ■ Disagree

Post

Agree: 27
Disagree: 0

Agree ■ Disagree