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

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

February 3–4, 2022

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

See Meeting Report #1, attached as Appendix B.

The Project

This is a summary of the second meeting of the Working Group ("WG") of approximately 30 expert stakeholders including scientists, clinicians, bioethicists, academics, lawyers, a consumer advocate, and individuals from the microbiome-based testing industry established for a grant (NIH #) exploring the regulatory frameworks for direct to consumer (DTC) microbiome-based health tests and whether that framework is adequate or overregulates this fledgling industry. (The full WG list is attached as Appendix B.)

Under the NIH grant, the WG is to 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.

The WG is to meet three times over a two-year period. On June 16–17, 2021, the study team convened the first WG meeting, held remotely over Zoom. The Meeting Report for that meeting was informed by the work already completed under the grant and is attached as Appendix A.

On February 3 and 4, 2022, the study team convened the second WG meeting, also held remotely over Zoom due to continued COVID-19 travel and meeting precautions. This report summarizes the second meeting.

Pre-Meeting Materials

Prior to the second WG meeting, participants were asked to review the agenda and the following background readings, which can also be accessed here:

1. Background on Regulation of Analytical Validity
2. Co-Investigator Recommendations for Regulation of Analytical Validity
3. Should you Get a Microbiome Test? NY Times Oct. 13, 2021
4. FDA website: Direct to Consumer Tests: https://www.fda.gov/medical-devices/in-vitro-diagnostics/direct-consumer-tests
5. Diagnostic Accuracy and Innovation Act Summary
6. 23andMe Personal Genome Service – Letter to 23andMe from FDA
7. "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations (Optional)

Meeting Agenda

DAY ONE

10:00 – 10:15
Welcome and Recap – Diane Hoffmann, JD, MSc, University of Maryland School of Law
10:15 – 10:30
Recommendations for Regulation of Analytical Validity – Diane Hoffmann & Jacques Ravel, PhD, Acting Director, Institute for Genome Sciences, University of Maryland School of Medicine
10:30 – 11:00
Discussion
11:00 – 11:45
Regulation of Medical Devices and DTC Genetic Tests – Gail Javitt, JD, MPH, Director, Hyman, Phelps & McNamara and Catherine Sharkey, JD, MS, Professor of Law, New York University School of Law
11:45 – 12:30
SMALL GROUP BREAKOUT SESSION
12:30 – 1:15 BREAK
1:15 – 1:45
Group reports.
1:45 – 2:20
Regulation of Software as a Medical Device – Areta Kupchyk, JD, Partner, Foley Hoag
2:20 – 3:15
SMALL GROUP BREAKOUT SESSION

DAY TWO

10:00 – 10:30

Reporting out of Small Group Discussion on Regulating DTC Microbiome-based tests as SAMD.
10:30 – 11:15
Regulation of Claims for Medical Devices by FDA and FTC – Frank Palumbo, JD, PhD, Professor and Executive Director, University of Maryland School of Pharmacy Center on Drugs and Public Policy and Rich Cleland, JD, Assistant Director, Division of Advertising Practices, Bureau of Consumer Protection, Federal Trade Commission
11:15 – 12:00
SMALL GROUP BREAKOUT SESSION
12:00 – 12:15 BREAK
12:15 – 12:45
Reporting out of Small Groups.
12:45 – 1:00
Wrap-up – Diane Hoffmann

Recap of Meeting #1

The first day of the WG meeting began with a welcome and recap of the first meeting, by **Diane Hoffmann, Project PI.** Prof. Hoffmann indicated that while the first meeting focused on the science of microbiome-based testing, this meeting would focus on regulatory issues. She recounted that at the end of the first meeting, WG members were polled regarding their views on the analytical validity of DTC microbiome-based tests and whether such tests should be more strictly regulated by CLIA. WG members were divided in their response to a question about the analytical validity of current DTC microbiome-based tests with a majority (56%) saying that "some are" but 41% saying "no" or they were "not sure." 93% said they thought the analytical validity of the tests could be improved; 48% thought CLIA should regulate the software algorithms used to generate and interpret genomic sequence data; 67% thought that regulators should require an external review component to evaluate a microbiome-based testing lab's evidentiary basis for performing a test or for the interpretive conclusions included in the test report.

Regulation of Analytical Validity

After the first WG meeting, a subcommittee was established to discuss the regulation of analytical validity. The subcommittee included Diane Hoffmann, Frank Palumbo, Barbara Evans, Daniel McDonald, Tharaknath Rao, and Felicia Langel. The subcommittee began with the understanding that analytic validity looks at sensitivity and specificity with respect to an analyte. Sensitivity relates to whether the test measures the smallest quantity of an analyte that can be reproducibly distinguished from background levels, while specificity looks at the ability of the test to detect only the analyte it is designed to measure.[1] In the context of microbiome-based tests, the analytical validity of the test would be based on ascertaining certain patterns of analytes (bacteria or bacterial DNA) in a sample and determining whether each analyte in the pattern is consistent with a reference standard. Metagenomic testing has the potential to be one assay that could detect "all" analytes present in a sample (i.e., untargeted) because it sequences

[1] By contrast, clinical validity looks at the sensitivity and specificity with respect to detecting an analyte that indicates a disease.

all the DNA of "all" bacteria in a sample. Specificity could be an issue though as the test could miss an analyte if it cannot detect a low abundance analyte).

The subcommittee then researched the current regulatory framework potentially governing the analytical validity of DTC microbiome-based tests. It found that, while CLIA and FDA regulations have standards that apply to DTC microbiome-based tests, they are general in nature and do not apply specifically to analytical validity in this context. For example, they require adequately trained personnel, recordkeeping, reporting, analytical validation, proficiency testing of high complexity tests and subject laboratories to inspection.

The subcommittee also acknowledged that CLIA certification is meaningless without proficiency testing to compare internal results to an external reference standard. Otherwise, a laboratory can be CLIA certified based on a paper inspection evaluating the laboratory's stated procedures, but analytical validity cannot be evaluated. At present, there is no standardized reference for microbiome composition, and no consensus as to what constitutes standard human microbiome composition. Laboratories can validate their tests internally by developing their own standards using specimens collected from their consumers, but tests cannot be validated externally across laboratories and testing platforms. NIST (the National Institute of Standards & Technology) is currently in the process of developing a reference standard using mock communities of bacteria, but it is likely years away from having a final result.

Scott Jackson, Group Leader, Complex Microbial Systems, National Institute of Standards and Technology, summarized the work being done by NIST. The microbiology program at NIST started in 2016, and NIST has now spent 6 years working to develop microbiome standards for clinical applications of the human microbiome. The goal of NIST is not to identify biomarkers associated with disease or certain diets. Instead, NIST focuses on measurement science to develop tools that can measure the accuracy and precision of analytical processes, which in turn allows public health organizations and academics to identify such biomarkers. The funding from FDA is for an infectious disease diagnostic group that looks at microbiome metagenomic testing as an untargeted pathogen detection tool.

NIST has developed DNA-based reference materials for about 20 microorganisms, which can be used to assess the accuracy of an analytical method. In addition, NIST is working to develop human fecal reference materials that mimic the human gut microbiome and are the most well-characterized human fecal material available. To do this, NIST collects fecal samples from a large number of donors in two cohorts. NIST chose cohorts of vegans and omnivores to capture different types of fecal material that could then be compared. The fecal samples from each cohort are then pooled, homogenized, and transferred into hundreds of aliquots. Cryomilling (cryogenic grinding) is used to reduce some of the matrix effects of different stool samples and normalize the composition of the reference materials. The aliquots are then frozen, at which point they are considered stable and frozen in time. NIST spends years characterizing the samples from both a microbiological perspective and a multi-omics perspective (for example, characterizing the small molecule metabolite outputs).

NIST also partnered with Jannsen, pharmaceutical companies of Johnson and Johnson, to do an international inter-lab study on metagenomic stool testing. NIST sent fecal samples to about 50

labs around the world and asked them to run metagenomic testing and return the results. NIST has spent a year and a half analyzing the data from that study and has found that there are a multitude of methodological variables which impact the results of metagenomic testing, including the sample collection method, DNA extraction method, library preparation method, and next generation sequencing instrument. This shows that it is important for laboratories to develop a workflow that eliminates changes in methodological variables in order to show that the workflow has analytical validity.

The subcommittee agreed that most DTC microbiome-based tests on the market today lack analytical validity, resulting in inconsistent results between different test platforms. This has caused what some have referred to as a "reproducibility crisis" that puts consumers at risk of harm, as inaccurate results may lead to self-misdiagnosis, delay in seeking medical treatment, and substituting non-medicinal supplements for prescription medications. The subcommittee developed the following recommendations to regulate analytical validity of DTC microbiome-based tests:

1) NIST should develop microbiome composition reference standards for human feces and should continue receiving government funding for this purpose.
2) Once NIST establishes reference standards, a robust reporting framework should be put in place to require companies to report how well their internally-developed standards compare to the reference standard or, alternatively, to send their results to an outside reference lab that is licensed or accredited to perform this service.
3) The NIST reference standards for microbiome-based testing should be incorporated into the CLIA certification program.

A more detailed description of the recommendations proposed by the subcommittee is attached as Appendix C. Prof. Hoffmann's PowerPoint presentation may be found here.

Dr. Jacques Ravel, Acting Director, Institute for Genome Sciences, University of Maryland School of Medicine, led the WG in a discussion of the subcommittee's recommendations.

One WG member noted the lack of FDA oversight in the recommendations and pointed out that if there is a robust reporting framework, the recommendations may need to touch on enforcement and which entity will be responsible for enforcing the reporting requirement. In the first WG meeting, the WG preferred the idea of a third party external review of these tests. This third party could be an organization similar to CAP (College of American Pathologists). If the test does not pass the third party review, one enforcement mechanism would be that the third party reviewer report the results to CLIA and FDA.

The WG discussed that CLIA certification of a laboratory, on its own, isn't enough to assure a test is analytically valid. Currently, these LDT tests can be performed by a CLIA certified lab. The laboratory certifies that its equipment and results should be consistent and are run under the standards set by CLIA. However, without any reference sample to externally compare those results, analytical validity cannot be determined.

One WG member questioned how to determine whether a laboratory's results are similar to the reference standard in the context of measuring hundreds of different species, and whether the data should be compared on the phylum or family level.

One WG member commented that some laboratories that state they are CLIA certified do not produce internally consistent results. The WG member observed that some labs reported different results when a sample was sent in duplicate. Reproducibility is part of the CLIA validation process, but this anecdote may indicate a lack of regulatory resources to enforce these issues. Thus, third party external review may be a more realistic solution. One member also pointed out that CLIA programs vary by state.

Some WG members commented that some microbiome tests report the detection of pathogens like *Helicobacter pylori*. If a test reports on a pathogen, the laboratory is regulated under CLIA and needs to validate the detection of that pathogen. A similar issue was seen with DTC genetic tests; 23andMe reported some genetic results that had known clinical significance, like BRCA1, along with results that did not. In that context, the FDA has since made clear that DTC predictive genetic tests are regulated as LDTs subject to the premarket approval process.

One WG member commented that when a pathogen is detected, the laboratory must have a protocol in place to deal with that information. Ideally, a laboratory should disclose the presence of a pathogen. Otherwise, the lab could potentially be liable for failing to disclose the result, and a clinician could not take steps to address the information. Another WG member added that many times a clinician only learns about the result when presented with a report from the patient. The report may include information on analytes that have known clinical significance, like pathogens, but also include information on analytes that have no known clinical significance, like enzymes, leaving the clinician unsure about the meaning and significance of the report. One suggested approach was for laboratories to include in the report a note stating that the test cannot determine the clinical significance of the detected pathogen and recommending a direct diagnostic test.

One group member commented that there is also a question of analytical validity in the research context because laboratories compare their results to studies done by other groups to evaluate the meaning of the results (for example, to make recommendations or predictions of disease). Thus, analytical validity is also important with respect to the data that one's results are being compared against. This concern calls out for a reference standard.

Regulating DTC Genetic Tests as Medical Devices

The next two presentations focused on the regulation of medical devices, and what the FDA has done to regulate DTC genetic tests as medical devices. First, **Gail Javitt, JD, MPH, Director, Hyman, Phelps & McNamara**, gave an overview of the regulatory framework of in vitro diagnostic (IVD) devices and LDTs.

IVD devices are products used by clinical laboratories to perform testing. These tests fall under the definition of a medical device in the Food, Drug and Cosmetic Act (FDCA) and the FDA's subsequent regulations. Like other devices, IVDs are regulated based on their level of risk, and

categorized into Class I, II, or III. Class I devices have the lowest risk, and, like all classes of medical devices, are required to follow general controls like registration and listing, reporting, record keeping, and good manufacturing practices. Class II devices are typically required to go through a pre-market review, like a 510(k) clearance (used when there is a predicate (similar product) already existing on the market), but are not required to go through the full pre-market approval process. Class III devices have the highest risk and are required to submit a pre-market approval application with clinical data to support the safety and effectiveness of the product. The FDA can also impose special controls on Class II or III devices. Penalties for non-compliance are imposed by statute, and can range from a warning letter to seizure, injunction, or monetary penalties.

By contrast, LDTs are tests performed in clinical laboratories using instruments, reagents, and the like, including IVDs. LDTs are regulated under CLIA and are largely exempt from FDA regulation. Over the years, the FDA's policy regarding LDTs has shifted. In the 1970s, the FDA excluded clinical laboratories from registration as a medical device manufacturer. In the 1990s, the FDA changed that policy and articulated its current policy of enforcement discretion—that the FDA has the authority to regulate LDTs because clinical laboratories can be manufacturers, but it has discretion not to enforce its regulations, and as a policy matter, largely would not do so. However, the FDA has typically regulated LDTs for test categories where the FDA has felt there was a high risk. Over the years, there have been proposals for a more comprehensive regulatory framework for LDTs, but none have been promulgated.

Key questions remain with respect to FDA regulation of LDTs. For one, there is no definition of LDTs in the federal Food, Drug and Cosmetic Act (FDCA) or regulations. The FDA had a draft guidance that said LDTs are tests that are developed, validated, and performed within a single laboratory, however that guidance never became final. Many LDTs do not fit this narrow description. Another question is whether the FDA has authority to regulate LDTs. The FDA argues that it has authority, that CLIA and FDA oversight are concurrent and complementary, and that notice and comment rulemaking is not required because regulation of LDTs would not be a fundamentally new regulation. By contrast, laboratories and other stakeholders argue that the FDA does not have authority because LDTs are proprietary procedures, not products, CLIA and FDA oversight are incompatible and conflict, and FDA regulation of LDTs would be detrimental for public health and economic policy reasons. In 2020, HHS expressed a policy that an LDT may meet the definition of a device, but the FDA could not regulate LDTs unless it engages in notice and comment rulemaking, and CLIA may be a sufficient framework for regulation in the absence of FDA oversight. However, in 2021, HHS changed its policy to again align with the FDA's enforcement discretion policy. Lastly, different stakeholders have different opinions about what the goal of regulation is. For some, it is innovation and flexibility. For others, it is safety, parity between IVD and LDT frameworks, and predictability for laboratories and other stakeholders.

Over the years, there have been legislative efforts to clarify the FDA's authority over LDTs, none of which have been enacted. Some have sought to strengthen FDA authority, while others have sought to remove FDA authority and enhance the role of CLIA. Others have proposed to create a new agency or organization within the FDA just to deal with IVDs. Some recurring

themes of those efforts have been to enact a risk-based oversight framework, easily allow test modifications, grandfather existing tests, and include a process for post market reporting.

Those who support strengthening FDA oversight argue: LDTs are unfairly and more lightly regulated than IVDs; there is an uneven playing field that disadvantages IVD manufacturers; there should be a single regulatory regime regardless of how the test is made; parallel regulatory regimes introduce distortions in the health care system and discourage FDA submissions; and the regulation of IVDs needs to be modernized. Those who oppose FDA oversight argue: LDTs are adequately regulated and CLIA oversight is sufficient; LDTs have not caused public health issues; LDTs provide needed flexibility for diagnostic testing; imposing FDA oversight will discourage innovation and reduce access to novel tests; and the FDA does not have the resources to handle a substantial increase in workload. (Gail Javitt's PowerPoint presentation may be found here.)

Catherine Sharkey, JD, MS, Professor of Law, New York University School of Law, elaborated on the regulation of DTC genetic tests as medical devices, using 23andMe as an example of FDA regulation in the DTC context.

In 2007, 23andMe began marketing its Personal Genome Service. It capitalized on an ambiguous regulatory landscape and operated a business model that was arguably designed to make clear that it was operating outside of the purview of a medical device that would be regulated by the FDA. The FDA became increasingly concerned about 23andMe, and in 2010 the Government Accountability Office reported that DTC genetic tests were misleading and of little or no use to consumers. The FDA sent letters to 23andMe and other large genetic testing companies notifying them that their tests qualified as "medical devices" subject to the FDA's premarket approval process. After DTC companies ignored these warnings, FDA sent cease and desist letters ordering them to immediately stop marketing and selling DTC genetic tests. Since then, 23andMe has conducted and submitted analytical validation for its tests, and, using *de novo* authorization and 510(k) clearances, the FDA authorized the tests with special controls. Concerns that FDA regulation will impede innovation and flexibility are countered by the fact that FDA has shifted to a more streamlined regulatory approach in the DTC genetic testing context.

Prof. Sharkey proposed that the FDA is not only a safety regulator of medical devices but is also a regulator of medical information. As part of its authorization of medical devices, the FDA requires data to determine the accuracy and reliability of a device, details about the developer's process and standards, and other information. Without FDA oversight, there is no basis on which the FDA can know who is manufacturing these tests and the prevalence of false positive and negative results. With the rise of DTC testing, this information is increasingly moving out of medical institutions and into the private sector. The FDA may serve as a more expert and accountable gatekeeper for these valuable genetic tests than commercial enterprises. Without this dataset, it is difficult to quantify the risks of DTC testing outside of relying on anecdotes, and academics and others seeking information are left to bargain with companies like 23andMe to receive access to datasets instead of working with public health organizations. If the FDA had gotten involved earlier in the DTC genetic testing arena, as it has with other medical devices, the information may not be in the hands of private companies.

According to Prof. Sharkey, FDA oversight may be needed to address the risk of providing consumers with incorrect or misleading information that they may use to make health-related decisions without the advice of medical professionals. Under the FDA framework, during premarket review, a developer must provide evidence that its test is both analytically and clinically valid. By contrast, CLIA focuses on only analytical validity. With these DTC tests migrating into the clinical sphere, CLIA may not be sufficient to address the risks from lack of clinical validity. FDA oversight may also more adequately address the risks of false positive or negative results. With respect to DTC testing, false positives may subject patients to unnecessary screenings, procedures, or medications, and false negatives may disincentivize medical follow-up or preventative measures by a patient and lead to premature death or avoidable illness. False negatives are of particular concern since false positives can be mediated by medical professionals, although false positives can lead to real harms and might put additional burdens on medical providers. The FDA can impose special controls to mitigate the risks of false positive or false negative results.

There are two recent legislative efforts that, if enacted, would have clarified FDA's oversight over these tests. The Diagnostic Accuracy and Innovation Act (DAIA), introduced in March 2017, would have classified DTC genetic tests as in vitro clinical tests, not as medical devices regulated by the FDA. FDA's oversight would have been limited to test development and manufacturing, but not laboratory operations or medical use and interpretation. This would hinder FDA in its ability to act as safety and information regulator because it would not be able to request raw data to further evaluate the analytical and clinical validity of tests. By contrast, the Verified Innovative Testing in American Laboratories Act, introduced in May 2021, would strengthen the FDA's authority. It would make clear that the FDA can continue to regulate LDTs. It would create a new umbrella category for LDTs and IVDs called "in vitro clinical tests," which would create parity between the two categories and preserve the FDA's existing risk-based framework. It would also require clinical laboratories to comply with certain new requirements, including adverse event reporting, and direct the FDA to create and maintain a database with information about the in vitro clinical tests available on the market. (Prof. Sharkey's PowerPoint presentation may be found here.)

Discussion

Following these two presentations, the WG discussed the risks of false positive and false negatives in the DTC microbiome context. Points made by members of the group included that false positives can be just as problematic as false negatives, and there can be psychological risks with false positives. For example, one WG member shared an anecdote that one patient had a microbiome result that suggested Lyme disease, which was treated by an alternative medicine partitioner for a year. The patient's symptoms were actually caused by a spinal cord tumor, which was left untreated during that time. Thus, a false positive can also result in a delay of medical treatment. One WG member also experienced patients who have requested a fecal microbiota transplant (FMT) based on DTC microbiome results. As drugs become more commercial, there may be a point where the only barrier to accessing these potent therapeutics are whether the insurance company will cover it. Patients may also seek medical treatment on their own by seeking products that are commercially available or attempting their own

treatments, like performing their own FMT. One WG member added that these companies sometimes spread a mistrust of the medical profession and encourage patients to self-treat. Another WG member added that it is not known what a healthy microbiome looks like, so it is difficult to determine what is considered unhealthy. Additionally, patients seek solutions, even though the proper way to intervene may not be known.

The WG also acknowledged that the examples of harms from false results are all anecdotal, which make it more difficult to measure the level of concern there should be about these tests. Thinking of the FDA as a regulator of medical information may be particularly important when considering the need to compile this information and develop data sets through reporting requirements.

The WG also discussed if the concept of false positive or false negatives means anything in this context where the test is not measuring a particular organism or disease but the microbiome composition. One WG member commented that, with respect to vaginal microbiome, the falseness of the results often relates to whether the results are actually related to the outcomes patients are concerned about. For instance, a patient may complain about vaginal burning, but it is not known whether the microbiome results are related to that symptom.

One WG member commented that there can be harms that come from the nutritional and dietary supplement recommendations often paired with the DTC microbiome results. Diet recommendations are not always benign. They may not be ideal in terms of nutritional value, and they may enhance eating patterns which are not healthy and can be deleterious in the long term.

One WG member asked how the FDA would regulate DTC companies that operate abroad, since there may be no physical product entering the U.S. to inspect. If a laboratory outside the U.S. is testing specimens from within the U.S., the lab would need a CLIA certification. With respect to FDA regulation, since laboratory test results are coming into the U.S., the FDA arguably would assert jurisdiction over a foreign lab for performing a medical device manufacturing function that is entering the U.S.

Breakout Session #1

For this breakout session, the WG members were asked the following questions:

1) Does the regulatory framework for medical devices adequately apply to DTC microbiome based tests? FDA treated 23andMe's Personal Genome Service Genetic Health Risk test as a Class II medical device. Should the DTC microbiome-based tests presumptively be subject to the Class II regulatory requirements, i.e., general and special controls? General Controls include the provisions of the Act pertaining to:
    a. labeling and promotion;
    b. device registration and listing;
    c. premarket notification or *de novo* submission;
    d. keeping of records and reporting to FDA; and
    e. good manufacturing practices.

Special controls include performance standards, post-market surveillance, and special labeling requirements.[2]

2) FDA does not regulate medical devices that it considers to be "low risk general wellness products." Will some DTC microbiome-based tests fit into this carve out? If so, what types of claims would be suitable for that exemption? FDA looks to marketing claims to determine whether a product meets this exemption. Claims can focus on a general state of health or a healthy lifestyle. Claims cannot make any reference to diseases or conditions unless they are healthy lifestyle claims and then they may state that they can help reduce the risk of certain chronic diseases or conditions or help living well with certain chronic diseases or conditions. These claims must be well understood and accepted by the scientific community or healthcare professional organizations.

3) Is the DAIA or VALID Act a better approach to regulation of these products?

Small Group Discussion

WG members generally agreed that the regulatory framework for medical devices had many facets some of which could be useful in regulating DTC microbiome tests, and that CLIA oversight alone was insufficient. Many WG members also agreed that oversight over clinical validity is needed, and the FDA regulatory framework could be useful for this. Some WG members felt that it was difficult to completely separate analytical validity and clinical validity, and so they must be dealt with together. Others felt that analytical validity and clinical validity could be separated, and that clinical validity was the most important. One WG member pointed out that there can be no clinical validity for these tests because it is not yet known what a "healthy" or "unhealthy" gut microbiome is and what the clinical significance of a particular result is. Thus, regulation may depend on what claims are made.

WG members discussed balancing regulation with innovation. Many WG members felt there was value in DTC microbiome-based tests. One WG member suggested requiring these tests to be ordered by a physician, but others felt there needed to be something between restricting the availability of the test and the oversight currently in place. Some members commented that the focus of regulation should be on gathering information because overregulation at this time could impede innovation.

WG members generally agreed that there needs to be some method of collecting information about DTC microbiome tests. There was a general consensus that FDA should be able to receive and compile information about adverse events and the companies that are offering these tests. One of the WG members who is a representative from a DTC microbiome company discussed that consumers often learn about these tests through social media and online spaces. One group member offered that another possible model is the framework for human cells and tissue-based products. There is no pre-market approval in that context, but those regulations incorporate the idea of notice in advance of marketing and some special controls.

[2] FDA can require additional compliance measures, including "patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions . . .), recommendations, and other appropriate actions as the Secretary deems necessary." 21 U.S.C. § 360c(a)(B).

The WG also discussed what constitutes an adverse event in this context. Many of the concerns with DTC microbiome-based tests are related to misinterpretation of the results and the actions consumers take because of that information. The potential harms do not always fit into what would typically be considered an adverse event from the product. For example, if a patient performs their own FMT based on microbiome test results, and then contracts a pathogen because their donor was not screened, there is a harm from the test, but it might not be considered an adverse event that is a result of the test result. It would be useful to have information about such events, but capturing this information may go beyond the regulatory avenues typically exercised by the FDA. The FMT industry established a registry to track FMTs performed Some WG members considered that there may be other agencies or third parties that are better suited to collect information.

Most WG members agreed that labeling and promotion should be regulated. For example, the FDA requires labeling for some genetic tests that warn, "This test is not a substitute for a visit to a healthcare provider, it is recommended that you consult a healthcare provider if you have any questions or concerns about your results" or, "This test does not diagnose any health conditions, results should be used along with other clinical information for any medical purpose." However, many breakout groups also discussed that these labels are not sufficient to mitigate risks, since consumers may not always pay attention to those labels. Some WG members also discussed that many tests already have some disclaimers, but they are in small font and not conspicuous. Thus, the typeface and placement of such disclaimers needs to be regulated. One breakout group also discussed that, to make this information more accessible, the report and its disclaimers would need to be offered in languages other than English.

Some WG members commented that it isn't clear what would constitute good manufacturing practices. A professional group like CAP may be best suited to develop and suggest good manufacturing practices. One group commented that the DTC test collection kits and process of specimen collection should be well-regulated by the FDA.

One breakout group discussed that NIST could play a useful role in this context. Scott Jackson discussed that NIST is one of two technical agencies within the Department of Commerce. NIST thus sees industry as its stakeholder, and its mission is to promote industrial innovation and competitiveness to keep the U.S. industries on the global competitive stage. It is very common for NIST to establish inter-agency agreements with other government agencies, including the FDA, EPA, and Department of Defense, to give NIST funding to develop standards relevant to those agencies. NIST is constantly getting requests and has limited resources to work on all the projects it is tasked with. Having dedicated funding for a particular project ensures that the project will be prioritized because NIST must meet the demands in the statement of work set forth in the inter-agency agreement. One breakout group added that there are other specimen sources, like vaginal and skin, that companies may test, and reference material may need to be developed for those sources as well.

Another breakout group discussed that there is another issue with respect to providers misinterpreting results. Regardless of whether the report comes to the provider directly or through the patient, the provider needs to be knowledgeable about interpreting the results in

order to be able to mitigate the risks. For example, even when more routine clinical tests detect *Clostridium difficile* in a stool sample, some clinicians misinterpret the result and treat for a C. diff infection inappropriately. It is important that clinicians understand these results so that they do not do the same with respect to DTC microbiome tests.

The WG did not come to a consensus on whether DTC microbiome-based tests could fit into the "low risk general wellness products" carve out. One group member suggested that if there are no health claims, there may not be a need to regulate at this time, but others thought that regulation should be proactive rather than reactive. WG members commented that it was difficult to draw a line between recreational and clinical use, especially since a consumer could believe they are receiving actionable health information, even if the test is marketed for general wellness use. One WG member suggested that whether a test is considered for recreational or clinical use may be useful in determining where a test falls in the risk-based classification. Some WG members suggested that one distinction is whether the test results would lead to treatment or not. Others thought this distinction was not useful because risks can occur even if the results would not lead to treatment. For instance, some WG members stated that dietary recommendations can carry risks, especially since, in most cases, consumers are seeking out these tests because they do not feel well. However, one WG member commented that in Los Angeles, some consumers seek out these tests for general wellness purposes. Another WG member distinguished tests that only report on microbiome composition from tests that include recommendations for dietary changes or supplements. Another group member felt that these tests should be regulated the same way because all results included in the report need to be valid.

The breakout groups generally did not have time to fully discuss the final question, but many WG members agreed that legislation would be useful to clarify the regulation of these products and provide clear and direct authority for the FDA to proceed with regulations in this area.

Regulating Software as a Medical Device

The last presentation of the first day of the meeting was by **Areta Kupchyk, JD, Partner, Foley Hoag**, who discussed the regulation of Software as a Medical Device (SaMD). FDA regulates software if it meets the definition of a device under the FDCA. There are two types of software in that category: (1) software that is embedded in a hardware medical device, and (2) software as a medical device, which stands alone from any hardware.

The definition of a device under the FDCA (as amended by the 21st Century Cures Act) excludes certain software functions listed in 21 U.S.C. § 360j(o). Some of those exceptions are for software that is not used for medical treatment or diagnosis, like administrative software or electronic patient records. Other exceptions are for medical software that is very low risk, like for maintaining or encouraging a healthy lifestyle. The healthy lifestyle exception likely does not apply here because the healthy lifestyle recommendations in DTC microbiome reports are too closely tied to the IVD test results. The fourth exception is for "transferring, storing, or displaying clinical laboratory tests or other device data" that is not "intended to interpret or analyze clinical laboratory tests or other device data, results, and findings."[3] DTC microbiome software likely does not fall under this exception since it is intended to interpret the test results.

[3] 21 U.S.C. § 360j(o)(1)(D).

The final exception includes "supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment," and "enabling such health care professionals to independently review the basis for such recommendations."[4] The main analysis under this exception is whether the healthcare professional can independently verify the results. If the healthcare professional cannot because the information is not available ("black box") or the analysis would have to bring together information from multiple sources that are not easily and independently gained, the software does not fall under the exception. The fifth exception does not apply if the software is "intended to acquire, process, or analyze a medical image or a signal from an [IVD],"[5] which DTC microbiome software likely does. For these reasons, DTC microbiome tests likely don't fall under any of the exceptions listed.

The regulation of SaMD is reflected in guidance documents where the FDA has interpreted the regulation of medical devices and IVDs as applied to software. Many of the key documents were published as a result of the FDA sitting as the chair of the SaMD working group for the International Medical Device Regulators Forum. Under these documents, SaMD is defined as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."[6] Software connected to a hardware medical device that is not necessary for a hardware medical device to achieve its intended medical purpose is considered SaMD and not an accessory to the hardware medical device. The guidance also makes clear that software uses an algorithm, including logic, sets of rules, models, or equations, to analyze data input like lab results, data, and reference materials, to produce an output intended for medical purposes.[7] The risks posed by SaMD are largely related to the risks of inaccurate or incorrect output, which may impact the clinical management of a patient.

Software can be for two intended purposes. For instance, one purpose may be to analyze the specimen, and another to analyze the results and make medical recommendations. It is unclear whether there would be two software products. The guidance also notes that SaMD is a medical device and includes IVD medical devices. It is unclear whether SaMD would be considered an integral component of an IVD or whether it would be regulated as a combination product. The guidance also states that SaMDs can be used in combination with other products, including other medical devices. Whether a product is a combination product or can be separated into multiple products may depend on how a manufacturer markets these products or, if pre-market approval is required, how a manufacturer presents the information to the FDA. If they sell separate reports, one for specimen results and another for analysis of the data, there may be two products. Typically, these DTC microbiome reports contain both test results and recommendations, which may mean they will be viewed as one product.

Software is unique from other medical devices because most software problems are traceable to errors made during the design and development process rather than manufacture and reproduc-

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[4] *Id.* § 360j(o)(1)(E).
[5] *Id.*
[6] IMDRF SAMD WORKING GROUP, SOFTWARE AS A MEDICAL DEVICE (SAMD): KEY DEFINITIONS 6 (2013), https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf.
[7] Among other things, the guidance includes as medical purposes, "providing information by means of in vitro examination of specimens derived from the human body." *Id.* at 6–7.

tion. Software involves the concept of branching, which is the ability to execute alternative series of commands based on different inputs. Branching contributes to the complexity of software programs and can hide latent defects until long after the software product has been introduced to the market. Software also requires continuous updates and changes to address bugs and issues, but those changes can introduce defects. The FDA recognizes that updating as a critical part of the oversight of the software. Software failures often happen quickly and without warning, and require quick responses, but those quick responses can convey a false sense of security that adequate corrections can be made easily. In actuality, quick responses are fraught with risk because more mistakes can be made. Because of the unique complexities of software, FDA has stressed that the development process for software should be "more tightly controlled than for hardware, in order to prevent problems that cannot easily be detected later in the development process."[8]

In order to determine the right controls to apply to mitigate risks associated with SaMD, we need to be able to categorize the risk. FDA has established two basic areas for categorization: (1) The significance of the information provided, which may be to treat or diagnose, drive clinical management, or inform clinical management, and (2) the healthcare situation or condition, which may be critical or life-threatening, serious, or non-serious. The significance of the information and the healthcare situation or condition helps to identify the risk category, as demonstrated in the table below. The table below reflects risk guidance found in FDA's guidance documents for SaMD, rather than classes of medical devices. Risk category IV is the highest risk category, with perhaps the highest level of regulatory oversight. The significance of the information and the healthcare situation or condition are found in the claims a company makes and in the indications for use of a product.

Significance of information provided / Healthcare situation or condition	Treat or Diagnose	Drive Clinical Management[9]	Inform clinical management[10]
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

Like IVD products, software must undergo verification, validation, and clinical evaluation. Software verification looks at whether the product is being built correctly by looking at objective evidence that the design outputs of each software development stage meet all the specified requirements when checked against its input specifications. Software validation looks at whether the user needs and intended use of the product is being met. Clinical evaluation looks for a valid

[8] FOOD & DRUG ADMIN., GENERAL PRINCIPLES OF SOFTWARE VALIDATION; FINAL GUIDANCE FOR INDUSTRY AND FDA STAFF 8 (2002), https://www.fda.gov/files/medical%20devices/published/General-Principles-of-Software-Validation---Final-Guidance-for-Industry-and-FDA-Staff.pdf.

[9] Infers that the information will be used to aid in treatment, to aid in diagnoses, to triage or identify early signs of a disease or condition, or will be used to guide next medical intervention (diagnostic or treatment).

[10] Infers that the information will not trigger an immediate or near term action, but rather may be used to inform of options for treating, diagnosing, preventing, or mitigating a disease or condition or to provide clinical information by aggregating relevant information (e.g., disease, condition, drugs, medical devices, population, etc.)

clinical association between the output of the software and the targeted clinical condition, along with analytical and clinical validation.

Depending on the risk of the device, software may be approved through premarket notification (510k), a *de novo* classification request, or a premarket approval application. When premarket submission is required, the FDA requires, among other things, software requirement specifications. This includes information related to the algorithms or control characteristics for therapy, diagnosis, monitoring, alarms, analysis, and interpretation with full text references or supporting clinical data. In this way, the FDA looks for a valid scientific association.

With respect to 23andMe's Personal Genome Service, the FDA found three primary risks: incorrect test results, incorrect interpretation of test results, and incorrect action based on test results. The FDA imposed special controls to mitigate those risks, including design verification and validation and labeling requirements. With respect to design verification and validation, the FDA required data to demonstrate analytical accuracy and reliability, and a user comprehension study to demonstrate that the intended user can use the device safely. The labeling controls included a clear description for how test results should be interpreted, supported by scientific evidence; descriptions of analytical performance; warning statements and limiting statements that the test does not diagnose health conditions and a patient should not use the results to change medication; and a prominent and conspicuous limiting statement that the test provides only a preliminary test results and needs to be confirmed prior to make any medical decisions. Other special controls included healthcare provider instructions for interpretation of results; publicly available and pre-purchase labeling; FDA approval for sample collection kits; and a prohibition on any labeling claim relating to supporting or sustaining human life, being of substantial importance in preventing impairment of human health, or preventing a potential, unreasonable risk of illness or injury. These special controls were imposed on 23andMe's Personal Genome Service test as a whole and were not specific to the software involved. (Areta Kupchyk's PowerPoint presentation may be found here.)

Breakout Session #2

The first day of the WG meeting ended with a breakout session on Regulating DTC Microbiome-based tests as SAMD. The WG members were asked the following questions:

> FDA has the authority to regulate software, whether it is standalone software or part of a medical device, if its intended use (function) meets the definition of a medical "device" under the Federal Food, Drug, and Cosmetic Act (FDCA). The 21st Century Cures Act amended the FDCA to exclude certain software functions from the definition of "device," including software that runs calculations or algorithms that a healthcare provider could independently verify. However, software functions that are "intended to interpret or analyze clinical laboratory test or other device data, results, and findings" are not exempted and thus fall within the scope of FDA's regulatory authority. FDA has exercised its authority to regulate software that generates interpretive genetic analysis reports that are provided directly to consumers. FDA views test results provided directly to consumers to pose a higher risk than results provided directly to a physician. FDA has imposed special controls to mitigate such risks.

1) What are the risks associated with providing microbiome test results/analyses directly to consumers (DTC)? In what ways, if any can these risks be mitigated?
2) To what extent should FDA regulate the software generating DTC microbiome-based test results? What types of risk mitigations (special controls), if any, should FDA recommend or require, apart from those for the hardware?
3) The special controls applied to 23andMe's Personal Genome Service focused on labeling requirements and design verification and validation, which included conducting a consumer comprehension study. Would such special controls be appropriate or sufficient to address risks posed by a DTC microbiome test?

The second day of the WG meeting began with a recap of the small group discussions. Several WG members commented that there were more questions than answers about how the regulatory framework might apply.

WG members thought that the main risks with providing microbiome test results directly to consumers relate to misinterpretation of the results and how consumers act on the results. If there is a false positive or false negative, or if the consumer misunderstands the result, the consumer may seek treatment that is unnecessary or fail to seek care from a medical professional. One WG member also added that there is psychological risk since consumers may worry about results, like pathogen detection, even though the results may have no clinical significance. One WG member commented that these reports are given less scrutiny than peer review for scientific publications, and yet the information is being sent directly to consumers, who act upon it.

The WG discussed that consumers tend to believe what they see in print, and these tests tend to impact the trust between the physician and patient when the physician has to convey that the information may be inaccurate. A lot of patients who seek these tests are dissatisfied with medical care in the first place. There is also an emotional connection for patients who are looking for an answer to chronic issues. One WG member noted that work is being done to understand how to approach patients and validate their emotions to restore that trusting relationship. One WG member added that many of the patients who order these tests have a sophisticated knowledge of science, and physicians are often unprepared to have in-depth conversations with those patients.

WG members discussed that there is risk associated with providers being unaware of how to interpret the results. As discussed in the first breakout group, physicians can also misinterpret or overinterpret results, like *C. difficile* detection, and inappropriately treat patients. By contrast, a well-trained physician can mitigate some of the risks of false positives or a patient's misinterpretation of results. However, WG members commented that many clinicians don't see value in any of these tests and don't have the time required to talk patients through these complicated issues.

One WG member commented that some companies have physicians as part of their network who are trained to interpret their results. Some WG members were skeptical that providers trained by a microbiome company could serve the role of educating consumers about the significance, or lack thereof, of the test results. One WG member commented that it depends on the company;

some companies connect consumers with independent providers, while others have their own providers that act more like a "rubber stamp" to tell the consumer the information is correct. That is the difficulty of the current market.

The WG discussed whether there may be an avenue for training physicians, or other providers, to how to interpret microbiome test results and convey that information to consumers. One WG member commented that work is being done to teach clinicians who are currently in school about interpreting microbiome test results. One WG member felt that microbiome tests currently have no clinical significance and thought that it was unrealistic to expect clinicians to learn how to interpret the results. The WG discussed whether genetic counselors may be trained to interpret microbiome tests, or whether a similar group of professionals can be created to do this interpretation.

One breakout group discussed that there are factors that have an important impact on whether software functions correctly. Changes in the input data, like a reference database, can have major implications on the test results. Some members commented that it was difficult to separate software from the rest of the process, and thus felt that the FDA would need to regulate the entire process as one. One WG also commented that consumers do not try to separate the software out from the product, so the FDA should not separate the software either.

Some WG members questioned how to identify risk categories for SaMD. They questioned who decides what is critical, serious, or non-serious; a patient or consumer might consider a condition serious, while a physician may think the condition is non-serious. They also noted that it may not be clear what the significance of the information provided is, since something that helps to diagnosis would also inform clinical management, and treatment may not change following a diagnosis. One breakout group discussed that there should be a uniform approach on how these tests fit within the categorizations set out in the table above.

WG members generally agreed that these tests should be regulated. Some WG members discussed whether there were entities outside the FDA to oversee design verification and validation of software. One WG member commented that the issue of whether there is oversight of software under CLIA is not resolved. The WG members discussed that a third party like CAP or the American Society for Microbiology might be an option. Scott Jackson commented that NIST and FDA currently have a "precision FDA program" to assess the analytical performance of software. NIST provides raw data, companies run the data through their software, and NIST then ranks the output based on quality and accuracy. To date, this is a voluntary program done as a competition, but it may be a pathway for regulation to evaluate the accuracy of software.

Many WG members thought that labeling special controls would be one way to mitigate the risk. However, WG members discussed that consumers don't always read labels, and that providing too much information can be confusing. WG members also noted that labeling probably would not be popular from a marketing perspective. Several WG members thought that consumer comprehension studies would be useful for microbiome tests to ensure that consumers could understand the labeling provided and the significance, or lack thereof, of the test results. One group discussed that there should be multiple comprehension studies to test whether consumers

still understand the test results at a later time. However, one WG member was not optimistic that consumers would be able to fully understand the results at this time.

One breakout group discussed whether there should be regulation of software writers for SaMD. The group discussed options like special training, certification, or submitting information on qualifications to FDA in the pre-market approval process. The group discussed that there are dangers in black box testing (where software is examined for its functionality without peering into its internal workings) because it cannot be determined what biases are built into the software. Latent defects can be caused by assumptions that were made upon building the software and complicitly applied. Therefore, it is important to have enough upstream checks to ensure those bugs are fixed before the product reaches the consumer. One WG also used the Theranos scandal as an example of the dangers of taking software at face value without questioning its inner workings.

Regulating Medical Device Claims

The next two presentations focused on the regulation of medical device claims. First, **Frank Palumbo, JD, PhD, Professor and Executive Director, University of Maryland School of Pharmacy Center on Drugs and Public Policy**, presented on FDA's regulation of medical device claims. The claims a company makes can determine how a product is regulated by the FDA. A product can cross the line and become an unapproved new drug or device with no change other than making claims related to disease.

The FDA has a number of tools to enforce action against manufacturers, including inspections, administrative sanctions like untitled letters, warning letters, recalls, and civil penalties, and judicial sanctions like seizures, injunctions, and criminal prosecutions. The FDA may also exercise enforcement discretion or issue regulations, guidance documents, and safety announcements to further its policies.

The FDA has taken a number of actions concerning claims for DTC tests. The FDA issued a number of untitled letters to companies selling DTC genetic tests that claimed to predict disease. The untitled letters notified the companies that their product requires FDA clearance, and that the FDA did not have a record of any such clearance. Untitled letters are often the first step in FDA action and are typically sent out prior to sending a warning letter. The FDA has also sent warning letters to DTC genetic test companies whose claims raised more serious concerns. For instance, the FDA sent a warning letter to DermaCare Biosciences when there were inconsistent claims about the product on its website. A warning letter was also issued to Inova Genomics when it claimed its test could predict patients' responses to specific medications, due to the seriousness of the public health risk. Warning letters are the last step in FDA's warning process and ignoring a warning letter will often result in further action by the FDA. The FDA has also issued safety alerts warning consumers about the risks of certain tests.

Device misbranding is a violation of the FDCA, and a device is misbranded if its label is false or misleading. Claims are deemed to be misleading if they fail to disclose certain information about the product's risk. The FDA has a guidance document on prescription and medical device promotional labeling. Promotional labeling is generally any labeling, other than FDA required

labeling, that is used for promotion of the product. Examples include printed, audio, and visual matter like brochures, booklets, mailing pieces, motion picture films, and more. Promotional labeling is separate from advertisement. Promotional materials (1) cannot be false or misleading, (2) must reveal material facts about the product, including consequences that can result from use of the product as suggested in the promotional piece, and (3) should present information about effectiveness and risk in a balanced manner. Advertisements are subject to different regulations. FDA guidance on consumer directed broadcast advertisement does not apply to devices. Advertisements of restricted devices (those that are required to be ordered by a physician) must contain a brief statement of the intended uses and warnings, precautions, side effects, and contraindications. Regulation of device advertisements is not enforced by the Office of Prescription Drug Promotion, but by the Center for Drug Evaluation and Research. (Dr. Palumbo's PowerPoint presentation may be found here.)

Following the presentation, the WG discussed that, although the FDA exercises enforcement discretion with respect to LDTs, the discretion may be narrowly applied to a specific issue that does not include claims. Also, the FDA has periodically departed from enforcement discretion to take action concerning DTC tests. The WG also discussed that claims are regulated differently based on whether they are structure-function claims or health claims. Both claims require FDA approval, but the standard the FDA applies is different. The group also commented that the FDA becomes aware of FDCA violations by searching for violations themselves and by competitors and others filing complaints with the FDA.

Rich Cleland, JD, Assistant Director, Division of Advertising Practices, Bureau of Consumer Protection, Federal Trade Commission, presented on FTC oversight of medical device claims.

Section 5 of the Federal Trade Commission Act prohibits deceptive and unfair trade practices in commerce. Section 12 prohibits false advertisement of food, drugs, cosmetics, and services. Between these two sections, false claims, unsubstantiated claims, and omissions of material fact are prohibited. The FTC's jurisdiction is concurrent with the FDA. FDA and FTC have a memorandum of understanding that the FTC has primary authority over the advertising of over-the-counter drugs, foods, cosmetics, and dietary supplements, while the FDA has primary authority over the labeling of drugs, foods, and cosmetics, and the advertising and labeling of prescription drugs. The distinction between advertising and labeling is not always clear. For instance, both the FDA and the FTC consider claims on a website where a product can be purchased to be within their respective jurisdictions.

An advertisement is considered deceptive if it contains a representation or omission of material fact that is likely to mislead a consumer acting reasonably under the circumstances and that representation is material to the consumer's purchase or use decision. A practice is considered unfair if it causes or is likely to cause substantial injury to consumers which is not reasonably avoidable by consumers and is not outweighed by countervailing benefits to consumers or to competition. These standards are used to require disclosures of risks.

An advertiser must possess and rely on a reasonable basis to substantiate objective advertising claims. If an advertisement makes an express or implied representation as to the level of support

the advertiser has for the efficacy of a product (for example, a claim the product is "clinically proven), then the advertiser must have at least that amount of evidence to support the claim. Claims implying scientific support require the level of evidence that experts in the field would require to demonstrate that the representation is true. When there is no indication of the level of support for a claim, the FTC looks at a number of factors, including the type of product, the type of claim, the consequences of a false claim, the benefits of a truthful claim, the cost of developing substantiation for the claim, and the amount of substantiation experts in the field believe is reasonable. Health claims must be substantiated with competent and reliable scientific evidence at the time of dissemination.

The FTC has not brought any cases involving microbiome DTC tests but did bring a claim against GeneLink Inc. for its DTC genetic test that generated a report recommending nutritional supplements and skincare products sold by the company. In that case, the FTC did not challenge the reliability of the genetic test but challenged the level of substantiation of the claims made, including claims that the disadvantages could be mitigated with nutritional supplements, that the supplements would reduce an individual's risk of impaired health or illness, and that the skincare product is scientifically proven to produce the effects claimed. The FTC also asserted that the respondents represented that their supplements treated or mitigated disease, like diabetes or heart disease, through use of testimonials. The FTC also alleged that the company did not use reasonable procedures to protect the genetic information of its customers.

With respect to microbiome tests, companies would be required to provide an evidentiary basis that confirms they are accurately measuring the analytes. Even absent an express claim on analytical validity, there is an implied claim of fitness for the intended use. If the company is also making nutritional recommendations or recommending supplements, probiotics, or other products, there is an implied claim that the recommendations will provide a beneficial effect, even if there is no express claim to that effect. Thus, claims regarding such recommendations will also need to be substantiated. Reference to specific diseases, express or implied cause and effect claims, and reports tied to the sale of other products will increase the level of substantiation required for microbiome test claims. The most important factor in determining the level of substantiation needed is the level of substantiation that experts in the field would require to support the claim. However, there does not seem to be a consensus on what is required in the microbiome context.

Rich Cleland outlined some of the claims that DTC microbiome test companies might make about their product, and categorized those claims from high risk, requiring the most substantiation, to no risk, requiring no substantiation. Among the high risk level were statements that claim to be supported by scientific proof or those that refer to specific conditions or diseases. Moderate risk claims may suggest some scientific basis but are more related to general wellness claims than disease. Low risk claims are those that are vague and where it is unclear how the consumer will interpret the statement. No risk claims are those that relate to the test more generally.

Microbiome test reports are unique because they can be viewed both as the product and the advertising. The report is considered advertising if it promotes the sale of products to address the health concerns raised. As a product, to meet the implied fitness for intended use, the results

must be valid and reliable based on existing scientific standards. As an advertisement, any express or implied performance claim for recommended products must be substantiated. (Rich Cleland's PowerPoint presentation may be found here.)

Breakout Session #3

The WG meeting ended with a final breakout session. WG members were provided with information regarding microbiome testing companies and the claims they make about the services they provide (attached as Appendix D). The groups were asked the following questions:

1) Review the claims made by DTC microbiome testing companies. Do any of them raise issues for regulation? How can these companies provide substantiation for their claims?

2) Is regulation of claims made by DTC microbiome-based tests adequate? Why or why not?

3) Are there alternative regulatory approaches that would ensure patients get accurate information about the tests and the results?

WG members agreed that many claims made by microbiome companies were problematic because they were related to health conditions or prevention, mitigation, or treatment of disease. One group commented that those claims need to be regulated more stringently, and currently are unsubstantiated. Many members commented that the companies were using creative phrasing to attempt to get around regulation. For example, some companies make claims about symptoms rather than diseases. Some companies claim the test is for someone with a particular condition, rather than claim the test can be used for that condition. Despite creative wording, WG members thought the FDA would regulate those claims. One group discussed that some marketing claims are for both the test and subsequent probiotics, which heightens the level of substantiation needed. WG members noted that recommendations for probiotics must be supported by scientific evidence.

Other claims were vague and undefinable, like claims that the results are "actionable," "healthy," and "unhealthy." One WG member commented that these claims are practically meaningless, and that companies are doing risk-reward calculations with their claims. They are willing to make somewhat false claims if the risk of the claim being challenged is low while the benefit of gaining customers may be high. Many WG members felt these vague claims are problematic because they imply the results can be used to make decisions about healthcare. Even when there were no recommendations or statements on how to interpret data, just providing data makes some implicit claim that the data is accurate and valuable. These implied claims may not be regulated under the FDA because the FDA has a narrow definition of health claims. However, while FDA typically considers physical safety risks, nothing precludes the FDA from considering economic risks to consumers. These implied claims are more likely to be regulated under the FTC Act because the FTC is more focused on whether the consumer would interpret the claims as health claims.

WG members discussed that until a company can show its results are analytically valid, no other claims can be substantiated. One group mentioned that there is no current definition of what a healthy gut is. Without a clear definition, the process cannot be validated, and thus the claims cannot be substantiated. One breakout group discussed that each laboratory test process needed to be validated on its own; the lab cannot rely on the work done by others to substantiate their claim without doing their own analytical and clinical validity testing. One WG member noted that insurance companies will be resistant to paying for tests that don't have evidence to support the results.

Many of the WG members felt that the regulations currently in place were an adequate foundation, but there are insufficient resources for enforcement. However, there were some areas where WG members thought regulations more specific to microbiome tests may be useful. For instance, specific regulations may need to address sample collection to prevent overgrowth or contamination, and disclosures may need to be required regarding the processes used to achieve test results and the usefulness of those results. One group discussed that different regulations may be needed to address the test itself, the algorithm software that produces diet or probiotic recommendations, and the claims made.

One group discussed that the FDA and FTC could be given alternative mechanisms to streamline enforcement of the regulations currently in place. Since issuing warning letters is a rigorous process, the group considered that the FDA and FTC might be able to enforce regulations more efficiently if they could impose fines for violations or if there were a mechanism for notifying companies there was a problematic claim without issuing a formal letter. One group discussed that professional associations may be an alternative means of regulation in the absence of resources for agencies to enforce their current regulations. They considered that an independent organization may provide a service that verifies whether the claims made are highly supported by evidence, moderately supported, or not supported at all. This would give consumers the ability to distinguish between microbiome tests, since currently consumers cannot differentiate between tests and identify which are better than others. The group questioned whether the industry would voluntarily participate in this sort of program, but also discussed that industries sometimes advocate for self-regulation to increase reputability. Some WG members discussed that tort actions and other lawsuits can be another way to regulate baseless claims, and threat of successful suits can lead to industry self-regulation.

The second WG meeting concluded by touching on the topics to be covered in the third meeting, including privacy, human subjects research, GINA, forensic applications, and possibly, insurance issues.

Appendix A
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Appendix C

Regulation of Analytic Validity for DTC Microbiome-Based Tests

Findings and Recommendations

At the conclusion of the first working group meeting on June 16–17, 2021, the principal investigator established a subcommittee to explore whether there is a generalized lack of analytic validity in DTC microbiome-based testing and, if so, what might be the regulatory approach for mitigating the problem. *Analytic* validity is the ability to detect or measure the analyte that the test is intended to measure. When laboratory instruments are unable to detect analytes of interest and/or microbiome composition (i.e., microorganism species or gene diversity and relative abundances) in a test sample cannot be accurately measured, DTC microbiome-based tests lack analytic validity.

The subcommittee met and agreed that most DTC microbiome-based tests on the market today lack analytic validity resulting in inconsistent microbiome-based test results from the same sample when different testing protocols are applied.[1] This has caused a "reproducibility crisis"[2] in the industry that may put consumers at risk of harm when they rely on inaccurate test results. These harms, for example, may include self-misdiagnosis, delay in seeking medical treatment, and substituting non-medicinal supplements for prescription medications.

1. Analysis of the lack of analytic validity in DTC microbiome-based testing.

The subcommittee considered why analytic validity is a problem in the DTC microbiome-based testing industry. The state of the art for measuring microbiome composition is by using next generation sequencing (NGS) techniques that amplify conserved genes (e.g., 16S rRNA) to selectively sequence the microbial DNA in a test sample, or that perform whole-genome shotgun sequencing of all DNA in the sample.[3] Testing laboratories choose which NGS methodology to use. It is this choice, and the associated ancillary testing protocols the laboratories select, that can lead to inconsistencies in test results from identical test samples.[4]

The bioinformatics pipeline for a microbiome-based test sample consists of various DNA extraction, sample collection, and sequencing techniques, as well as "software components, databases, and . . . hardware and operating system[s]" used to analyze the sequenced data.[5] These tools, which are routinely used in the DTC microbiome-based testing industry, are not comparable across laboratories because techniques have not been benchmarked and best practices have not been identified.[6] Although standardizing the bioinformatics pipeline would help address the problem of reproducibility in microbiome-based testing, these tools are still evolving and as others have pointed out, settling on a certain set of techniques "too early [can stifle] a field's growth and lock[] researchers into seeing only what the current techniques reveal."[7]

Alternatively, reproducibility in microbiome-based testing would be greatly aided by having "certified or accredited reference reagents . . . widely used by the field.'"[8] To measure the microbiome composition of a test sample, component organisms are detected and identified by analyzing sequencing data against a well-characterized reference database.[9] Most microbial species, however, lack annotated reference genomes because taxonomy changes over time as microbes combine and mutate. Consequently, the datasets that are available for sequence comparison are incomplete.[10] Although there are analytical strategies that can be used to account for an incomplete reference database and to "determine which taxa are [] present in a sample," such strategies (e.g., filtering out low abundance sequence reads from a dataset) also "risk[] rejecting species that are actually present."[11]

2. Recommendations for regulatory oversight of analytic validity in the DTC microbiome-based testing industry.

Although there is evidence that some DTC microbiome-based testing laboratories are attempting to establish standards, including reference databases,[12] they are not validated against widely accepted reference standards because these do not currently exist. Establishing reference standards requires acquiring test samples from larger and more representative populations than the commercial entities use. Such large-scale efforts are underway or have been initiated by organizations including the Microbiome Quality Control (MBQC) project,[13] the International Metagenomics and Microbiome Standards Alliance (IMMSA),[14] and the National Institute of Standards and Technology (NIST). Standards development specifically overseen by the government, i.e., NIST, would ensure that the microbiome-based bioinformatics pipeline and associated reference databases are fully standardized and that these standards are adopted by the industry.

The subcommittee recommends that:

1) NIST, which is currently funded by FDA should develop microbiome composition reference standards for human feces,[15] and should continue receiving government funding for this purpose.

2) After NIST establishes reference standards, a "robust reporting framework"[16] should be put in place to require companies to report how well their internally-developed standards compare to the reference standard(s). Further, companies should be required to report how they measure the analytic validity of their tests, i.e., what are their testing methodologies and what algorithms are they using. Here, DTC microbiome-based testing laboratories would be required to use a "lockdown method" that ensures internally consistent test results by utilizing an analytical algorithm and reference database that does not change until the accumulation of new data necessitates the development of a "version 2.0" of these tools.[17]

> As an alternative to this internal assessment, we could recommend that the DTC microbiome-based testing companies send their results to an outside reference lab that is licensed or accredited to perform this service.

3) Finally, the NIST reference standards for microbiome-based testing should be incorporated into the Clinical Laboratory Improvement Amendments of 1988 (CLIA) certification program overseen by the Centers for Medicare and Medicaid Services (CMS). The current CLIA certification process ensures that laboratory tests not cleared or approved by FDA are analytically validated in a laboratory's own environment before results using the test can be released to consumers.[18] Under a revised CLIA framework, DTC microbiome-based testing laboratories would be required to seek CLIA certification that evaluates the testing methodologies they are using and how well their test results compare to the reference standard.

Appendix D

DTC Microbiome-Based Testing Companies

COMPANY	DESCRIPTION	CLAIMS
Aperiomics https://www.aperiomics.com/our-services/aperiomics-xplore-microbiome/	Aperiomics uses deep metagenomic sequencing to identify microorganisms in any test sample. Although the company markets to consumers, it sends the sample collection kit directly to the clinician for collection. Results are also sent to the clinician for interpretation.	*Aperiomics Xplore-MicroBiome can characterize any known microorganism in any sample.* *Clinically actionable data for healthcare providers.* *Extensive datasets that lead to meaningful results for researchers and institutions.*
Atlas Biomed https://atlasbiomed.com/uk/microbiome	Atlas Biomed is a U.K. company that states it does not market in the U.S. The company obtains a stool sample using a DTC collection kit and analyzes both the type (i.e., composition) of gut microorganisms present and the relative abundance of genes present in these microbial communities (i.e., function).	*What you will learn:* • *Your microbiome health score and protection from 5 disease risks.* • *Proportion of probiotics and beneficial bacteria, micronutrient synthesis potential and diversity score.* • *Weekly personalized food recommendations to improve your microbiome health in 17 areas.* • *List of bacteria found in your microbiome (%) and what enterotype you belong to.*
BIOHM https://biohmhealth.com/collections/gut-testing	BIOHM markets a variety of probiotics, prebiotics, and immunity supplements. The composition and function of the gut microbiome is analyzed from a DTC stool sample collection kit.	*Test your gut and receive actionable recommendations on how to optimize your digestive health.* *The BIOHM Gut Report is the most comprehensive sequencing available to consumers.* *The final report is reviewed by a Microbiome-Trained Registered Nutritionist who will provide wellness recommendations to*

		balance your overall digestive health.
Biomes https://biomes.world/en/	Biomes is a German company that uses both conventional culturing techniques and metagenomics to analyze the composition and function of the gut microbiome from a DTC stool sample collection kit. The company provides personalized dietary recommendations and markets dietary supplements under their "BIOM.uniq" brand.	*Understand intestinal complaints.* *Detect immunodeficiencies.* *Reduce weight problems.* *Analysis & recommendations based on scientific findings.*
Carbiotix https://carbiotix.com	Carbiotix is a Swedish company that markets prebiotics, medical foods, and disease therapeutics to consumers in Europe and the U.S. Its OneGut test measures the level of gut microbes over time using a DTC stool sample collection kit containing multiple sample vials.	*Carbiotix mission is to increase the consumption of prebiotics in people's diets.* *Carbiotix reliable, low-cost consumer gut health testing platform OneGut is offered exclusively through our LinkGut service to food & beverage, supplement and pharmaceutical companies, as well as providers of health and wellness services interested in highlighting the benefits of prebiotics.* *LinkGut allows a company to offer their own customised and dedicated gut health testing service to their customers.*
DayTwo https://www.daytwo.com	DayTwo is an Israeli company that targets pre-diabetic and diabetic patients for its gut microbiome analysis. Using a stool sample from a DTC collection kit and a patient-provided hemoglobin A1C blood test result, the company prepares a personalized glycemic profile that predicts the patient's glycemic response to foods.	*DayTwo's science empowers clinicians and people with diabetes, providing a food-as-medicine approach to manage glucose levels and improve overall health.*

Elsavie https://elsavie.com/en/home/main	Elsavie is an Estonian company that measures the composition of the gut microbiome using a DTC stool sample collection kit. The company provides dietary recommendations and, for additional purchase, four types of fiber supplements. Also, for an additional charge, a nutritionist will explain the test results and create a personalized nutrition plan.	*Who should take the test?* *Obviously, if you're curious about what's going on inside your gut, then this test will tell you and help to prevent chronic diseases.* *But if you're:* • *overweight* • *underweight* • *on a special diet* • *about to start, or have finished an antibiotic treatment* • *experiencing discomfort* *then the test will illuminate what you can do to improve your health through dietary changes.*
Evvy https://www.evvy.com/	Evvy has yet to launch and is currently accepting consumers to its online waitlist. The company will offer a DTC vaginal microbiome-based test using an at-home vaginal swab collection kit. Although not clear from its website, the company may also offer probiotics and supplements to consumers.	*Get unprecedented insight into your health with Evvy's at-home vaginal microbiome test.* *We'll tell you if research indicates that your microbes are associated with broader health outcomes like recurrent UTIs, yeast infections, mycoplasma/ureaplasma, and BV, fertility challenges, preterm birth, STI acquisition, and more.*
i-screen https://www.i-screen.com.au/	i-screen is an Australian company that limits its services to registered users in Australia. The company offers a variety of laboratory tests at a collection center, but it also markets a DTC microbiome-based test using an at-home stool collection kit. The company combines fecal microscopy with metagenomic sequencing to analyze the composition and function of the gut microbiome. For an additional charge, the company provides a nutritionist to interpret the test results and recommend a nutrition plan.	*This holistic picture provides actionable insights to help you improve your gut health.* *In this assessment, our Nutritionist will interpret your results to identify the key dietary and lifestyle adjustments and supplemental support to help you improve your health and wellbeing.*
Juno Bio https://www.juno.bio/	Juno Bio is a U.K. company that markets a DTC vaginal	*The only comprehensive vaginal microbiome test you can take*

	microbiome-based test. The kit includes a swab for vaginal sample collection and a pH applicator, and consumers consult with a "vaginal coach" to discuss the results of their analysis.	*without ever even putting your shoes on. Brought to you by the world's leading vaginal microbiome scientists.*
Microba https://insight.microba.com	Microba is an Australian company offering a DTC stool sample collection kit for use in measuring gut microbe composition and function.	*Learn about your microbiome's diversity levels, which gut bugs are present and what they can do.* *Get evidence-based ratings on your gut's potential to produce vitamins and other important substances.* *Discover where you sit on the gut health spectrum and learn how to promote the growth of friendly bacteria.* *Book a Microbiome Coach phone consult and talk through your findings with a practicing dietitian or nutritionist.*
OME https://ome.health	OME is a U.K. company that preferentially markets in the U.K; it collects stool, saliva, and blood samples using DTC collection kits. The company provides a 12-week personalized nutrition coaching program from a gut microbiome composition and function analysis and, for an extra charge, includes genetic and metabolite analyses.	*We harness the power of your gut microbiome and other health data to deliver a personalised plan to address your nutrition needs.* *Your dedicated coach will prepare recipes based on your individual nutritional needs. Shoppable with major retailers.*
Onegevity https://www.onegevity.com	Onegevity offers several DTC tests including one using an integrated stool, blood, and saliva sample collection kit. Its microbiome-based test, Gutbio, analyzes the composition and function of the gut microbiome from a stool sample to make personalized dietary recommendations.	*Who is this test for?* • *Individuals experiencing constipation or diarrhea* • *Those experiencing symptoms of excessive gas, bloating, abdominal pain, nausea* • *Individuals with frequent heartburn* • *Individuals who have a family history of IBS or IBD*

Psomagen https://psomagen.com/gutbiome/	Psomagen is the U.S. subsidiary of South Korean Macrogen Corporation. The company offers combined gut microbiome and genetic analyses using a DTC stool and saliva sample collection kit. The company also offers a standalone gut microbiome analysis (i.e., composition and function) for personalized dietary recommendations.	*When you provide a stool sample for the gut health test, we use whole metagenome sequencing to:* • *Analyze the microorganisms in your gut* • *Tell you about your microbe profile, metabolism, nutrition utility, lifestyle status, and gut type* • *Provide you with a full probiotics profile* • *Offer custom dietary suggestions to implement based on your metabolism and microbiome*
smartDNA https://www.smartdna.com.au	smartDNA is an Australian company that markets (primarily to Australian users) a variety of tests including a gut microbiome analysis (i.e., composition and function) and genetic testing. A clinician must order the DTC stool sample collection or saliva detection kit (for genetic testing), or the consumer may order the kits and select a health care professional contracted by the company. The test results are then sent to the health care professional who interprets them for the consumer.	*Your smartGUT™ insights includes:* • *How your microbiome sample compares to our healthy population.* • *The level of diversity in your microbiome sample is a key indicator of health. An average to high microbial diversity is associated with a healthier microbiome.* • *A dysbiosis compass which maps the imbalance between the types of bacteria present in your gut microbiome.* • *The ratio of the two main microbiome groups which correlates with obesity.* • *Learn how old your gut microbiome is. Includes your gut age relative to your chronological age.* • *Dietary profiling of your gut microbiome to determine how your*

		dietary intake is affecting your microbiome.
Smart Nutrition https://smartnutrition.co.uk/	Smart Nutrition is a U.K. company that markets internationally. The company offers a variety of laboratory tests including a DTC gut microbiome-based test and a DTC vaginal microbiome-based tests. The DTC gut test includes a stool sample collection kit to collect five stool samples over three consecutive days, and the DTC vaginal test includes a vaginal sample collection kit to obtain one non-menstruating vaginal sample.	*Digestive testing provides important information about the state of your digestive health and is a sensible place to check when your health is struggling or if you are suffering from digestive symptoms. The Vaginal microbiome Profile is the most comprehensive evaluation available. This test will be useful for women who have or are at risk of pregnancy and fertility issues, bacterial vaginosis, candida, pelvic inflammatory disorder and other vaginal problems.*
Sun Genomics https://sungenomics.com	Sun Genomics markets a personalized probiotic under the name Floré. After a consumer returns the DTC stool sample collection kit, the company analyzes the composition and function of the gut microbiome, makes dietary suggestions, and customizes the probiotic. The company also markets its custom probiotic to infants and children.	*We create custom gut probiotics tailored and formulated to your unique microflora to improve your digestion, increase your energy, and reduce bloating; helping you perform at your best.* *Floré personalized probiotics help with your [baby's; toddler's; kid's] digestive issues, food allergies and overall gut health.*
Thryve https://www.thryveinside.com	Thryve manufactures a personalized probiotic and makes dietary recommendations. From a DTC stool sample collection kit, the company analyzes the composition and function of the gut microbiome and formulates a custom probiotic.	*What are the benefits?* • *Supercharge weight loss & fat burn so you can look and feel great.* • *Improve digestion so you can live life free of bloating, abdominal pain, diarrhea, and constipation.* • *Modulate your autoimmunity so you can remove the frequency and severity of flare ups.* • *Improve your mood so you can stay*

		motivated to accomplish your goals. • *Increase energy levels so you can be at 110% with your significant other, children, and co-workers.*
uBioDiscovery https://ubiodiscovery.com	uBioDiscovery is a Canadian company that markets to residents of Canada and makes personalized dietary recommendations using a pre- and post-gut microbiome analysis ("SUPERBIOME"). The DTC collection kit contains a 30-day supply of probiotics and two stool sample vials that are returned to the company before and after the consumer completes the probiotic trial.	*SUPERBIOME is optimal for those who are trying to lose weight, anyone who has a chronic condition like IBS or IBD, or if you are simply looking to improve and maintain your overall health.*
Verisana https://www.verisana.com	Verisana offers a wide variety of health tests including hormone, STI, and gut health analyses using different types of biological samples. The gut health test consists of a gut microbiome composition and function analysis using a DTC stool sample collection kit. Specialty analytes, such as zonulin and *H. pylori*, are measured at an additional cost.	*The gut is our "second brain" – which is why bowel health plays a crucial role in our general well-being.* *Our Comprehensive Gut Biome & Health Test helps you to get a comprehensive picture of your gut health as the state of your gastrointestinal system is extremely important for your overall well-being.*
Viome https://www.viome.com	Viome markets custom prebiotics, probiotics, and supplements and makes dietary recommendations. The company analyzes the composition and expressed function of the gut microbiome using metagenome and metatranscriptome	*We go below the surface to understand your unique biology and make it easy for you to get the nutrition your body needs with a custom-made supplement, probiotic + prebiotic formula.* *Our Gut Intelligence Test analyzes your microbial gene expression and includes over 20 subscores related to inflammation, microbial activity,*

	technologies from a DTC stool sample collection kit.	*richness & diversity, gut lining health, and more.* *The nutrition recommendations included with this test target the underlying cause of inflammation in your gut microbiome and represent the first step in improving your gut health!*
Wellnicity https://www.wellnicity.com	Wellnicity offers custom vitamin packs and other supplements after the consumer consults with a company clinical nutritionist about their gut microbiome results. The company provides a DTC collection kit for stool and saliva samples, and the stool samples are analyzed using both NGS and culture techniques.	*Basically, if you're experiencing gastrointestinal issues that have you concerned about your gut health, this may be the gut health test you've been looking for.* *Gut bacteria symptoms and imbalances . . . are all indicative of poor GI tract issues. Armed with your test results and a wide range of gut health products, Wellnicity can help get you back on track.*