

Meeting Report

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

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

October 17–18, 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

This is a summary of the third meeting of the Working Group (“WG”) of approximately 35 expert stakeholders, including scientists, clinicians, bioethicists, academics, lawyers, consumer advocates, regulators and individuals from the microbiome-based testing industry, established to explore the adequacy of current regulatory frameworks for direct to consumer (DTC) microbiome-based health tests. This meeting and the prior two meetings were supported by NIH award # 1R01HG010571-01. The full WG participants list is attached as Appendix A.

Under the NIH award, the WG was established 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 has met 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 report for that meeting was informed by work that had already been completed under the grant, including a white paper describing the DTC microbiome-based testing industry and the potential regulations governing the industry as well as the results of a series of focus groups with researchers, clinicians and consumers about their knowledge and attitudes about these tests. The summary of the meeting can be accessed [here](#).

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. The second meeting report can be accessed [here](#).

On October 17 and 18, 2022, the study team convened the third and final WG meeting. The third meeting was held in a hybrid setting with some participants meeting over Zoom and some participants meeting at the University of Maryland Francis King Carey School of Law. This report summarizes the third meeting.

Pre-Meeting Materials

Prior to the third WG meeting, participants were asked to review the agenda and the following background readings, which can also be accessed [here](#):

1. Catherine M. Sharkey, *Direct-to-Consumer Genetic Testing: The FDA's Dual Role as Safety and Health Information Regulator*, 68 DEPAUL L. REV. 343 (2019), <https://via.library.depaul.edu/cgi/viewcontent.cgi?article=4086&context=law-review>.
2. David A. Simon, Carmel Shachar & I. Glenn Cohen, *Skating the Line Between General Wellness Products and Regulated Devices: Strategies and Implications*, 9 J. L. & BIOSCIENCES 1 (2022), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9280986/pdf/ljac015.pdf>.
3. David A. Simon, Carmel Shachar & I. Glenn Cohen, *At-home Diagnostics and Diagnostic Excellence: Devices vs General Wellness Products*, JAMA 2022;327(6):523-524 (2022), <https://jamanetwork.com/journals/jama/article-abstract/2788407>.
4. Letter from Courtney H. Lias, Dir., Div. of Chemistry & Toxicology Devices, Food & Drug Admin., to Adam Odeh, Regul. Affs. Manager, 23andMe (Jan. 23, 2019), https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180028.pdf (outlining special controls for 23andMe's pharmacogenetic assessment system).
5. Valerie Gutmann Koch, *Recreational Genetics or Research Enterprise? Cloudy Consent Issues Arising from Direct-to-Consumer Genetic Testing*, BILL OF HEALTH (Aug. 2, 2018), <https://blog.petrieflom.law.harvard.edu/2018/08/02/recreational-genetics-or-research-enterprise-cloudy-consent-issues-arising-from-direct-to-consumer-genetic-testing/>.
6. Felicia M. T. Lewis, Kyle T. Bernstein & Sevgi O. Aral, *Vaginal Microbiome and Its Relationship to Behavior, Sexual Health, and Sexual Transmitted Diseases*, 129 OBSTETRICS & GYNECOLOGY 643 (2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6743080/pdf/nihms-1049888.pdf>.
7. Catherine Roberts, *The Privacy Problems of Direct-to-Consumer Genetic Testing*, CONSUMER REPS. (Jan. 14, 2022), <https://www.consumerreports.org/dna-test-kits/privacy-and-direct-to-consumer-genetic-testing-dna-test-kits-a1187212155/>.
8. Jake Holland & Daniel R. Stoller, *With Congress Quiet, States Step in to Safeguard Genetic Privacy*, BLOOMBERG L. (Sept. 1, 2020), <https://news.bloomberglaw.com/privacy-and-data-security/with-congress-quiet-states-step-in-to-safeguard-genetic-privacy>.
9. Jessica L. Roberts & Jim Hawkins, *When Health Tech Companies Change their Terms of Service*, 367 SCIENCE 745 (2020), https://www.science.org/doi/epdf/10.1126/science.aaz6732?adobe_mc=MC MID%3D784513131

[86454640573221364775136889922%7CMCORGID%3D242B6472541199F70A4C98A6%2540AdobeOrg%7CTS%3D1672521073](https://www.casematrix.com/cases/86454640573221364775136889922%7CMCORGID%3D242B6472541199F70A4C98A6%2540AdobeOrg%7CTS%3D1672521073).

10. *Lowe v. Atlas Logistics Grp. Retail Servs. (Atlanta), LLC*, 102 F. Supp. 3d 1360 (N.D. Ga. 2015), <https://casetext.com/case/lowe-v-atlas-logistics-grp-retail-servs-atlanta-llc>.

11. *GINA and the Case of the “Devious Defecator”*: *Broad Prohibition Impacts Nonprofit Employers*, VENABLE LLP (June 8, 2015), <https://www.venable.com/insights/publications/2015/06/gina-and-the-case-of-the-devious-defecator-broad-p>.

12. Cynthia Marietta & Amy L. McGuire, *Direct-to-Consumer Genetic Testing: Is it the Practice of Medicine?*, 37 J. L., MED. & ETHICS 369 (2009), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2795579/pdf/nihms151713.pdf>.

Meeting Agenda

DAY ONE

11:00 – 11:30

Welcome and Review of Second Working Group Meeting – Diane Hoffmann, JD, MS, University of Maryland School of Law

11:30 – 12:45

SMALL GROUP BREAKOUT SESSION #1 – Application of Medical Device Regulatory Framework to DTC microbiome-based testing industry

12:45 – 1:30 Lunch

1:30 – 2:00

Reporting out of Small Group Breakout Session #1

2:00 – 3:00

SMALL GROUP BREAKOUT SESSION #2 – Application of Special Controls to DTC Microbiome-based testing companies

3:15 – 3:35

Is DTC microbiome-based testing human subjects research or should it be treated as such? What should be required in terms of regulation? – Mary-Claire Roghmann, MD, MS, Professor of Epidemiology and Public Health and Medicine, University of Maryland School of Medicine

3:35 – 3:50

Discussion

3:50 – 4:00 Break

4:00 – 5:00

Secondary harms that may result from DTC microbiome-based testing:

- I. Can test results be used to stigmatize individuals? – Larry J. Forney, PhD, MS, University Distinguished Professor, Department of Biological Sciences, University of Idaho
- II. Can microbiome test results be used to determine identity? – Jacques Ravel, PhD, MSc, Acting Director, Institute for Genome Sciences, University of Maryland School of Medicine
- III. Other issues: Can test results affect insurance coverage or access? Can companies misuse data or use data without consumer consent?

6:00 Dinner

DAY TWO

10:00 – 10:15

Reporting out of Small Group Breakout Session #2

10:15 – 11:00

Consumer Privacy and Third-Party Use of Data – Natalie Ram, JD, Professor of Law, University of Maryland Carey School of Law

11:00 – 12:00

SMALL GROUP BREAKOUT SESSION #3 – Secondary Harms from Use of DTC microbiome-based test results

12:00 – 12:30 Lunch

12:30 – 1:00

Reporting out of Small Group Breakout Session #3

1:00 – 1:20

State Regulation of DTC Microbiome Testing – Jennifer Herbst, JD, LL.M., MBIO, Professor of Law and Medical Sciences, Quinnipiac University School of Law, Frank H. Netter MD School of Medicine

1:20 – 1:45

Discussion

1:45 – 2:00

Wrap-up – Diane Hoffmann

Recap of Meeting #2

Professor Diane Hoffmann, Project PI, recounted that at the second working group meeting presenters gave a broad overview of FDA regulation of medical devices and software as a medical device (SaMD), as well as FDA and FTC oversight of claims. Professor Hoffmann indicated that the third WG meeting would provide participants with the opportunity to elaborate on the issues raised at the second meeting and delve deeper into how these regulatory frameworks apply, or should apply, to DTC microbiome-based tests.

At the second meeting, WG members generally agreed that the regulatory framework for medical devices had many facets that could be useful in regulating DTC microbiome-based tests, and that CLIA oversight alone was insufficient to address the risks posed. WG members also agreed that labeling and promotion should be regulated, and that there should be a method of collecting basic information about these tests such as what DTC microbiome-based tests are currently available and the name of companies selling these tests to the public. However, some members cautioned that the clinical significance of microbiome composition is not yet known, and that over-regulation can impede innovation.

Updates Since Meeting #2

- **Change in companies selling DTC microbiome-based tests**

At the first WG meeting, WG members were given a list of DTC microbiome-based testing companies and their claims that had been put together by the project staff. Since that meeting, Day Two was removed from the list because it changed its business model and now only sells its test kit through organization health plans; it no longer sells tests directly to consumers. Professor

Hoffmann explained that this may indicate that some industry participants are evolving and changing their business model to shift more into the diagnostic space. Additionally, [GI Map](#) was added to the list. Additional companies will be added or removed as the project staff finds that changes are warranted.

- **FDA revision to guidance on regulating Software as a Medical Device**

The FDA revised its framework for clinical decision support software in its final guidance document issued on September 28, 2022. The FDA abandoned the risk categorization framework from the International Medical Device Regulators Forum, which had been a significant source of confusion. The final guidance introduces a new, narrow interpretation of the statutory exclusion of software from the definition of a medical device under 21 U.S.C. § 360j(o)(1)(E). That exclusion states that a software product is not a medical device if it is:

- (1) not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system (section 520(o)(1)(E) of the FD&C Act);
- (2) intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines) (section 520(o)(1)(E)(i) of the FD&C Act);
- (3) intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition (section 520(o)(1)(E)(ii) of the FD&C Act); and
- (4) intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient (section 520(o)(1)(E)(iii) of the FD&C Act).¹

The guidance introduces additional definitions, including new, narrow interpretations of statutory terms “medical information about a patient” and “other medical information.” The guidance states that the “FDA interprets *medical information about a patient* to be the type of information that normally is, and generally can be, communicated between [health care professionals] in a clinical conversation or between [health care professionals] and patients in the context of a clinical decision, meaning that the relevance of the information to the clinical decision being made is well understood and accepted.”² The FDA “interprets *other medical information* to include information such as peer-reviewed clinical studies, clinical practice guidelines, and information that is similarly independently verified and validated as accurate, reliable, not omitting material information, and supported by evidence.”³ The guidance states that software that “provides a specific preventative, diagnostic, or treatment output or directive or that addresses a time-critical decision” would not satisfy the statute’s device exclusion criteria.⁴

¹ U.S. FOOD & DRUG ADMIN., CLINICAL DECISION SUPPORT SOFTWARE – GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 6 (2022), <https://www.fda.gov/media/109618/download>.

² *Id.* at 9.

³ *Id.*

⁴ *Id.* at 12.

These new provisions broaden the scope of software that FDA considers subject to the medical device regulations and will likely prove controversial.

Regulatory Flowchart

Professor Hoffmann presented a flowchart to assist the group in analyzing whether DTC microbiome-based tests would be regulated as a medical device based on the information learned in the second WG meeting and FDA’s revised guidance. She asked the group whether it was accurate and helpful. The original flowchart with some modifications is depicted below in **Figure 1**.

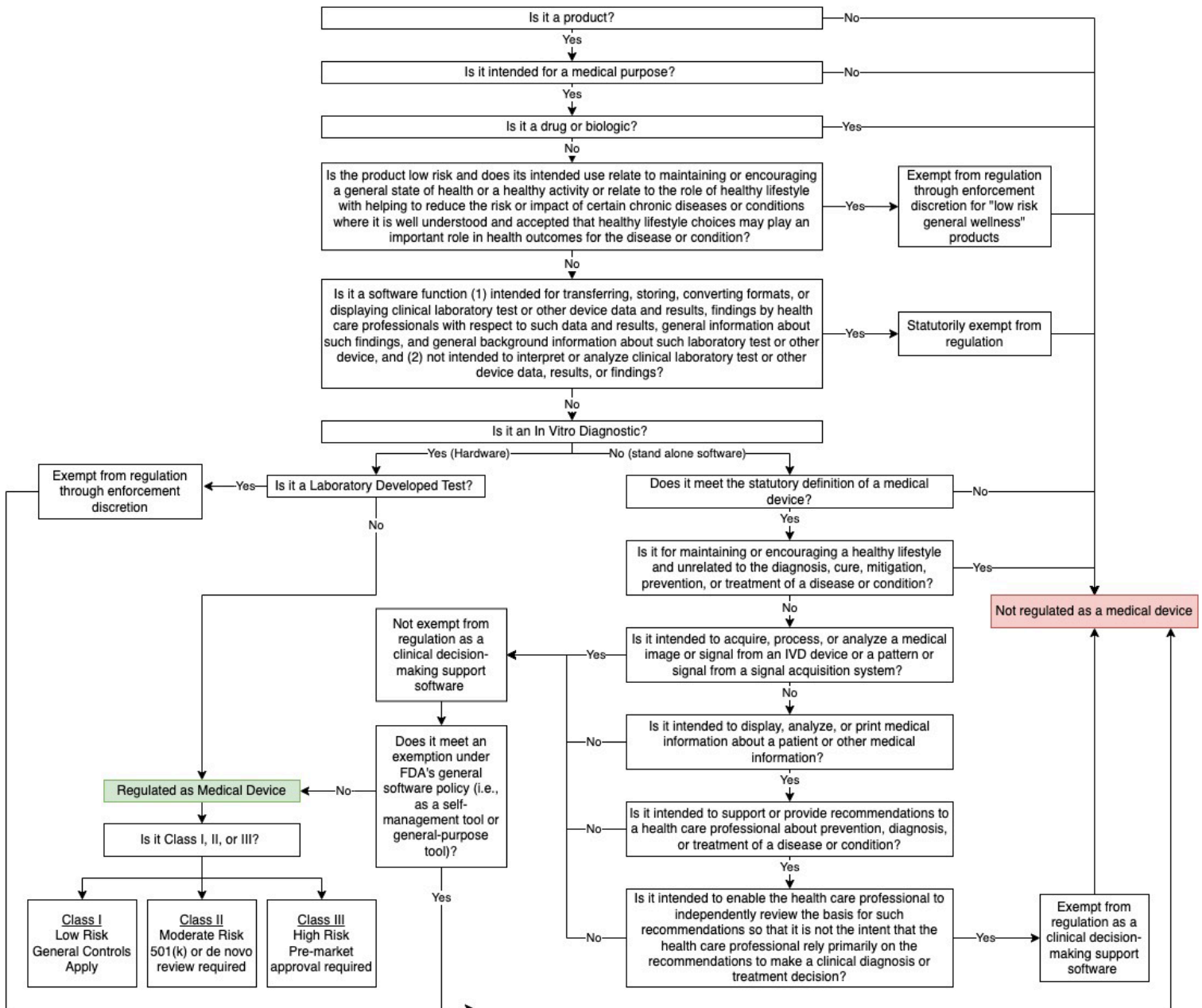


Figure 1. DTC Microbiome-based Testing Regulatory Flowchart

To understand whether a product falls under the exemption for “low risk general wellness products,” it is useful to look at the examples of general wellness and non-general wellness claims in FDA guidance.⁵ Importantly, general wellness products are products that have “(1) an intended use that relates to maintaining or encouraging a general state of health or a healthy activity, or (2) an intended use that relates the role of healthy lifestyle with helping to reduce the risk or impact of certain chronic diseases or conditions and where it is well understood and accepted that healthy lifestyle choices may play an important role in health outcomes for the disease or condition.”⁶ General wellness claims for products in the first group “**do not make any reference to diseases or conditions.**”⁷ By contrast, general wellness claims for products in the second group can mention a disease if the relationship between the lifestyle recommendation and the disease or condition is generally accepted and supported by evidence in the scientific community. The FDA also provides examples of these healthy lifestyle claims that mention diseases or conditions.⁸

In general, FDA intends to exercise enforcement discretion for software functions that “[h]elp patients (i.e., users) self-manage their disease or conditions without providing specific treatment or treatment suggestions” or “[a]utomate simple tasks for health care professionals.”⁹

With respect to DTC microbiome-based tests, Prof. Hoffmann suggested that the software used to analyze sample composition, to compare compositions to a reference or average from the dataset, to draw conclusions from the comparison, and to make recommendations, should all be considered part of the test that could potentially be regulated as a medical device.

Prof. Hoffmann’s PowerPoint presentation may be found [here](#).

Breakout Session #1

In the first breakout session, WG members were asked to consider the following actions and answer the related questions:

1. Review the flow chart for determining if DTC microbiome-based tests would be regulated as medical devices. Identify any issues with accuracy. Determine if DTC microbiome-based tests would be exempt from regulation as a medical device and, if so, where they would fall out on the flow chart.
2. Should both the test and the reports generated from the tests be regulated? If so, should they be regulated differently? What if a company provides consumers with no recommendations but provides only the test results, i.e., composition of microbiome?

⁵ U.S. FOOD & DRUG ADMIN., GENERAL WELLNESS: POLICY FOR LOW RISK DEVICES – GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 2–4 (2019), <https://www.fda.gov/media/90652/download>.

⁶ *Id.* at 3.

⁷ *Id.* at 3 (emphasis in original).

⁸ *Id.* at 5.

⁹ U.S. FOOD & DRUG ADMIN., POLICY FOR DEVICE SOFTWARE FUNCTIONS AND MOBILE MEDICAL APPLICATIONS – GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 13–14 (2022), <https://www.fda.gov/media/80958/download>.

3. Should these tests be subject to the general controls applicable to all medical devices, including Class I (lowest risk?) These include:
 - a. Applications of provisions in the FD&C Act prohibiting adulteration;
 - b. Application of provisions in the FD&C Act prohibiting misbranding;
 - c. Device registration and listing;
 - d. Premarket notification;
 - e. Authority to ban certain tests due to substantial deception or potential for injury;
 - f. Notification and repair, replacement, and refund;
 - g. Recordkeeping and reporting requirements;
 - h. Restricted use of device if deemed to pose a substantial risk; and
 - i. Good manufacturing practices.

WG member were directed to go to the FDA website <https://www.fda.gov/medical-devices/regulatory-controls/general-controls-medical-devices> for more information about each of these.

When working through the flowchart, WG members agreed that whether a DTC microbiome-based test falls under the regulatory framework for medical devices depends on the claims made and level of risk involved and must be decided on a case-by-case basis. WG members suggested that some components of DTC microbiome-based tests would fall under medical device regulation while other components, on their own, would not. Multiple WG members commented that the FDA will look at all the components of the test together when determining whether there is a medical device.

WG members felt that DTC microbiome-based tests are intended for a medical purpose. However, WG members pointed out that there may be other intended purposes, like research. For example, many people send samples to the American Gut Project to participate in citizen science, not for medical purposes. One group stated that the FDA looks at the company's intended purpose, rather than the consumer's intended purpose. A company can show intent through its claims or through its advertisements or promotions that exhibit an intended medical purpose, even if it is not said explicitly. For example, an advertisement that shows before and after pictures exhibiting weight loss may illustrate an intended treatment effect, even if not explicitly stated.

WG members thought that, based on the claims made, some tests would fall under the general wellness category, while others would not. Whether a statement is a general wellness claim is unclear when terms like "dysbiosis" and "abnormal" are used. In the gut microbiome context, there is no literature defining what constitutes dysbiosis and whether it is connected to or the cause of disease. In the vaginal microbiome context, however, there is literature that dysbiosis is associated with certain disease states, although there is not a clear causal relationship.

While the words "healthy" or "abnormal" do not point to any particular disease, consumers often understand these terms as being related to sickness or disease. Thus, it is not clear whether claims that use these terms are "structure-function" claims or disease claims. The WG also discussed that recommending a particular diet may or may not be considered a treatment depending on the information provided and the claims made. If the recommendation is accompanied by a claim that the changed diet will prevent or treat disease, for example, obesity,

the diet would be considered a treatment. By contrast, if the recommendation is accompanied by a claim that the diet will promote a healthy lifestyle, the diet would *not* be considered a treatment. Also, if a report from a company merely provides educational information, e.g., generally accepted and scientifically supported statements that eating a certain way is statistically likely to improve your overall health, it is likely to be exempt from the regulatory framework, however, if it directs the consumer to take a specific action, such as eating a specific food or supplement without scientific evidence supporting the relationship between consuming the food/supplement and overall health, it would likely not be exempt.

WG members also thought that DTC microbiome-based tests would not fall under the exemption for “transferring, storing converting formats . . . [etc.]” because the software is “intended to interpret or analyze clinical laboratory test or other device data, results, or findings.”

Some WG members thought that DTC microbiome-based tests would likely be considered in vitro diagnostics (IVD). These WG members reached this conclusion because the test analyzes a specimen. The software involved, even if it would not be considered an IVD on its own, is likely to be considered embedded in the hardware because FDA would look at all of the components of the test as one. WG members thought that some of these tests are developed as laboratory developed tests (LTDs), while others are not.¹⁰

Once it is determined that a test falls under medical device regulation, one WG member said that, as a practical matter, the test likely would fall under Class II. The FDA tends to be conservative, and the legal default for a new product is Class III. In theory, it is possible to petition to classify a novel product as Class I, but in practice it is unlikely. Companies can likely prove that DTC microbiome-based tests are not high-risk products, i.e., Class III, but the classification will probably only be reduced to Class II, not Class I.

A reorganized version of the flowchart incorporating comments from WG members and further research is depicted below in **Figure 2**. The revised flowchart now begins by asking whether the product meets the definition of a medical device, and then asks whether the product is exempt from regulation as a low risk general wellness product. From there, the questions diverge based on whether the product is an in vitro diagnostic or software product. Exemptions from regulation as a medical device under the 21st Century Cures Act¹¹ now fall under the branch for software products.

¹⁰ One group discussed that DTC microbiome-based tests are not LTDs because sample collection is done at home and outside the lab. The location of sample collection likely is not relevant to whether a test is an LTD or not because sample collection ordinarily happens outside the lab and outpatient stool samples are almost always collected at home. The FDA’s 2014 draft guidance, though abandoned in 2017, defined an LTD as an IVD “intended for clinical use and designed, manufactured, and used within a single laboratory.” U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY, FOOD AND DRUG ADMINISTRATION STAFF, AND CLINICAL LABORATORIES – FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOP TESTS (LTDs) 5 (2014), <https://www.fda.gov/media/89841/download>. Sample collection likely does not fall within “design, manufacture, or use.” The draft guidance states that an IVD would not be an LTD if a third party created a specialized specimen collection kit, but does not touch on the specimen collection itself. *Id.* at 6.

¹¹ 21 U.S.C. § 360j(o)(1)(E).

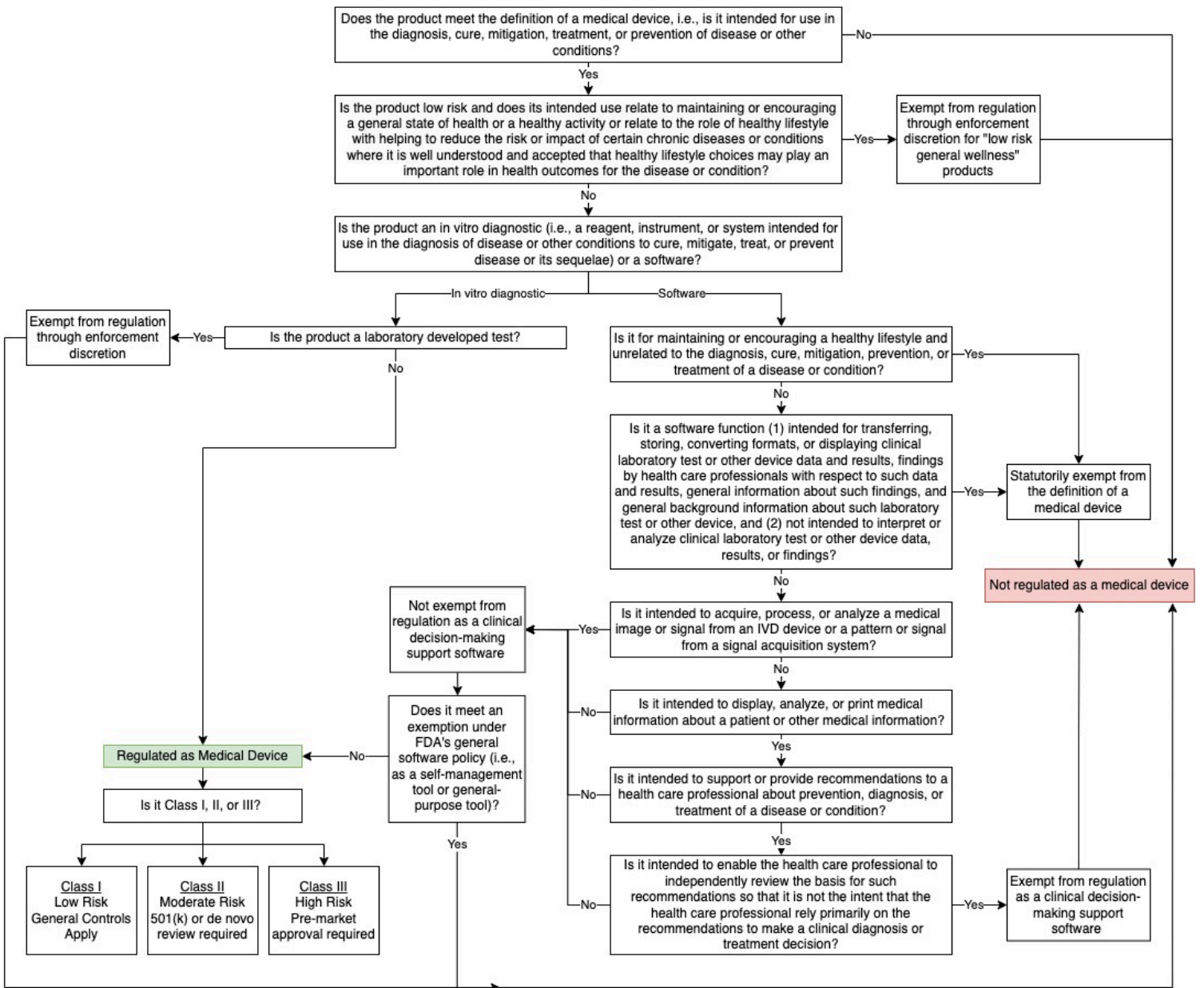


Figure 2. Reorganized DTC Microbiome-based Testing Regulatory Flowchart

WG members thought that whether the test’s report generated should be regulated differently than the test itself would depend on the recommendations and claims included in the report. WG members felt that if a report provides recommendations related to diagnosis or treatment of a disease, then that report should be regulated differently than a report that only gives a consumer their microbiome composition results. One group asserted that there is market pressure for companies to include recommendations because consumers are not satisfied with simply knowing their microbiome composition; consumers want to know what actions they can take to improve their health. Yet, these recommendations make the tests more concerning and potentially harmful.

WG members thought that these tests should be subject to general controls if they meet the definition of a medical device and do not fall into any exceptions. The exception for general wellness products may apply for DTC microbiome-based testing companies that only make general wellness and healthy lifestyle claims. One breakout group questioned whether general controls should apply even if the test fell into the general wellness exception.

Breakout Session #2

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

1. Should any of the special controls required for the 23andMe Personal Genome Services (referred to by FDA as Genetic Health Risk Assessment Systems) be required for DTC microbiome-based tests? (see list of specific controls attached as Appendix B).
2. Should these tests be subject to adverse event reporting? What would constitute an adverse event?

One group noted that the risks identified by the FDA with respect to 23andMe's personal Genome Services—risk of incorrect understanding of the device and test system, incorrect test results like false positives and negatives, and incorrect interpretation of the test results—apply equally to DTC microbiome-based tests. WG members felt that DTC microbiome-based tests should be required to include the following limiting statements:

- 1) the test may not enumerate all the microorganisms in the user's gut or vagina and the microbiome may change over time (i.e., your microbiome can be different tomorrow);
- 2) the detection of a pathogen does not necessarily indicate disease, and the absence of a pathogen does not mean that the pathogen is not present;
- 3) there is insufficient evidence to link the gut microbiome to any disease or harmful condition or a predisposition to any disease or condition, the test is not intended to diagnose disease or to be used in medical decision-making;
- 4) the test should not be used for certain purposes, for example, prenatal testing or determining predisposition for cancer;
- 5) some people may feel anxious about obtaining test results;
- 6) there are limitations to the test, for example, test results may be affected by external variables like low sample quantity or issues with sample collection, shipping, storage or collection buffers;
- 7) there is an FDA approved collection device that should be used,¹² or that no FDA approved collection device is available.

One group also noted that requiring a frequently asked questions page may be helpful as this is standard for diagnostic tests.

Some WG members felt that a statement to seek advice from a physician may not be appropriate in this context because there is no evidence linking the gut microbiome composition to disease. Physicians may not understand the test results and may treat people unnecessarily when

¹² For gut microbiome sample collection FDA has approved the OMNIgene+GUT Dx OMD-200 system by DNA Genotek.

attempting to respond to the report. Also, the physician did not order the test and does not have access to data supporting the validity of the test. One WG member said that lawyers at his institution worry that acting on such results could lead to malpractice claims.

Several groups discussed which providers may be able to interpret these tests in the future. Physicians may be trained to interpret tests, dietitians may be able to analyze how they relate to diet, or genetic counselors could take their experience with human genetic testing and apply it to microbiome tests.

One group thought that some of the limiting statements imposed on 23andMe may not be possible for DTC microbiome-based testing companies to make. For instance, a company may not be able to explain how to interpret the test results if the information is not being used for medical purposes. A company may not have information about performance characteristics or specific criteria for test result interpretation and reporting. Additionally requiring the company to provide studies showing a link between the results and certain clinical outcomes is problematic when no causal relationship has been established and there is no intervention available. However, this lack of data begs the question of whether the test should be permitted to be marketed at all if it can't provide the required information, or if it should simply be required to disclose to consumers that it does not have data connecting the test results with health conditions or outcomes.

One group discussed that while there is currently no evidence linking the microbiome with clinical outcomes, more information may be available in the future. Whatever framework is imposed needs to be flexible enough that it can be updated on a regular basis.

The WG acknowledged that too much information can overwhelm the consumer and may not be productive. Also, consumers may not be able to interpret and understand information relating to the probability of test failure. One group highlighted the importance of having information written in plain language and in a way that is understandable to a lay user. Another hypothesized that companies may use limiting statements to reduce liability by saying consumers were warned about the issue, even if consumers do not actually read or understand the information.

Additionally, adding requirements like a study about consumer comprehension could be helpful but may stifle innovation. Some WG members were less concerned with stifling innovation because they felt that DTC microbiome-based testing companies are not contributing to the public domain but rather they are benefitting from their consumer data. Others expressed that many bad companies entering the market make it more difficult for legitimate market participants.

Only one breakout group discussed whether DTC microbiome-based tests should be subject to adverse event reporting. The group felt that these tests can pose harms if they delay diagnosis, so they should be subject to adverse event reporting. Manufacturers should be required to report death, serious injury or harm, or a threat of death or serious injury or harm to the FDA. The manufacturer should also investigate complaints about adverse events.

Human Subjects Research

Mary-Claire Roghmann, MD, MS, Professor of Epidemiology and Public Health and Medicine, University of Maryland School of Medicine, gave an overview of the regulation of human subjects research. 45 C.F.R. § 46.102(e) defines “human subject” as “a living individual about whom an investigator . . . conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.” To qualify as “research,” two components must be met: There must be (1) “a systematic investigation, including research development, testing, and evaluation,” that is (2) “designed to develop or contribute to generalizable knowledge.”¹³ While there is no formal definition of “systematic investigation” or “generalizable knowledge” their dictionary definitions and ordinary usage informs the understanding of these terms. The dictionary defines “systematic” as having a method or plan and defines “investigation” as a detailed or careful examination or exploration, or to learn the facts about something complex or hidden. A systematic investigation develops or contributes to “generalizable knowledge” when the information produced is intended to be shared with others, for example, through publishing. However, quality improvement projects, though they may be shared throughout a hospital or facility to improve services, would not be considered contributions to generalizable knowledge.

Whether DTC microbiome-based testing companies are performing human subjects research depends on what the companies do with the data obtained. The company may create a biobank—a biological collection of human, animal, plant, or microbial samples that are associated with sample data. Well run biobanks are managed according to professional standards. There are several benefits to biobanking. The stored samples and data may be used to develop products and services to promote public health, foster cross-collaboration between disease advocacy organizations and research scientists, and hasten research by reducing the need for individual researchers to collect specimens. However, there are associated ethical challenges, including informed consent, ownership and commercialization, and confidentiality.

Under HHS regulations, to satisfy informed consent requirements, the subject must be provided with “[a] statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures that are experimental.”¹⁴ There must also be a statement that the “subject may discontinue participation at any time.”¹⁵ In addition, the Belmont Report, a report written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to identify basic ethical principles and guidelines, says “[r]espect for persons requires that subjects, to the degree they are capable, be given the opportunity to choose what shall or shall not happen to them.”¹⁶

¹³ 45 C.F.R. § 46.102(l) (2021).

¹⁴ 45 C.F.R. § 46.116(b)(1).

¹⁵ 45 C.F.R. § 46.116(b)(8).

¹⁶ NAT’L COMM’N FOR THE PROT. OF HUM. SUBJECTS BIOMEDICAL & BEHAV. RSCH., DEP’T OF HEALTH, EDUC., & WELFARE, THE BELMONT REPORT 6 (1974), https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf.

The unique nature of biobanks makes it difficult to meet these informed consent requirements. Biobanks are not used for a single research endeavor but are resources used in many projects. They are future-oriented and often created without knowing what research they may be used for in the future, making it difficult to say what the purpose, length of participation, and procedures to be followed will be. Biobanking may also involve data about people other than the research subject, for example, human genetic data can be used to obtain information about genetic relatives of the subject. Allowing subjects to discontinue participation at any time or choose what happens to their samples may be logistically difficult for biobanks. Not all work done with biobanks constitutes human subjects research; for example, work with deidentified¹⁷ samples is not considered human subjects research. However, although it is permissible to use deidentified samples without consent, the subject must be told that the sample will be deidentified and may be used for research purposes.

There are four informed consent models that biobanks may use: opt-in, opt-out, tiered consent, and broad consent. The opt-in consent model looks similar to a typical informed consent document, providing information about the biobank, its purpose, how to participate, the benefits and risks, etc. The company asks the patient or consumer for their consent to participate in the biobank, and the company must keep track of which patients or consumers agreed to participate. The opt-out consent model notifies patients that when they receive services through the company, the records and samples may be used for research purposes unless the person takes the affirmative act to opt out of participation. The tiered consent model allows participants to review the research projects that seek to use the biobank and choose the research projects for which they will permit their samples and data to be used. This model requires rigorous tracking by the company to ensure that the samples and data are only used in the projects for which that person consented. Finally, broad consent is a newer model of consent whereby participants give consent for their specimens and data to be used in future, unknown projects. When broad consent is obtained, subsequent use or storage of identifiable specimens and data does not require additional consent, so long as all the requirements of broad consent are met, including limited review by an Institutional Review Board (IRB). Implementing broad consent requires the company to have a system for monitoring who has given broad consent and who has not. This requires a seamless information technology system that can track broad consent, refusal to consent, and revocation of consent over the lifetime of a person.

Broad consent became possible in January of 2019 when the revised Common Rule went into effect. The revised Common Rule regulations expressly permit researchers to obtain broad consent for “storage, maintenance, and secondary research uses” of “identifiable biospecimens.”¹⁸ Broad consent requires additional information to be provided to the subject beyond the typical requirements of informed consent,¹⁹ including (1) “[a] general description of the types of research that may be conducted”; (2) a statement that the sharing of identifiable information or biospecimens may occur; (3) a description of the length of time that information and biospecimens will be stored, or that the period of time is indefinite; (4) a statement that the

¹⁷ Deidentified means that the sample cannot be connected to identifying information.

¹⁸ 45 C.F.R. § 46.116(a). “Secondary research” refers to research that uses already existing data, which may be done in the future and not be known at the time of data collection.

¹⁹ 45 C.F.R. § 46.116(d).

data may be shared with other groups; (5) a statement that clinically relevant results may not be disclosed to the subject; and (6) an explanation of who to contact should the subject want to revoke their consent. In addition, if an individual refuses to give broad consent, an IRB cannot later waive consent for any reason.²⁰

The presentation also included an example of a microbiome-based testing company's Terms of Service. BIOHM's [Terms of Service](#) require consumers to agree to the terms in order to receive microbiome testing. The Terms of Service include elements of broad consent: They include information on how individual-level information and aggregated, de-identified information will be used; a statement that the customer allows the company to access and analyze the stored, deidentified samples using the same or more advanced technology; and a statement that deidentified samples will be stored indefinitely while identified samples will be stored for up to ten years. The terms also require a consumer to waive property rights to their specimen. BIOHM also has a [Consent to Participate in Research](#) form where consumers may consent to specific research studies. This form looks more like a full informed consent document and follows the new Common Rule regulations. BIOHM uses this form for research that it intends to publicize or publish in a peer-reviewed scientific journal.

Mary-Claire Roghmann's PowerPoint presentation may be found [here](#).

Discussion

Following the presentation, the WG discussed whether DTC microbiome-based testing companies are performing human subjects research. The WG thought that the "human subjects" criteria are met because the tests analyze a biospecimen. However, the "research" criteria may not be met because the investigation may not be intended to contribute to generalizable knowledge. Additionally, if deidentified information is used, the use may not be considered human subjects research.

If the company plans to use the information to publish, then there would be intent to contribute to generalizable knowledge. By contrast, if the information is used to do quality improvement or for other internal purposes, then there would not be intent to contribute to generalizable knowledge. One WG member commented that the key inquiry is in the intent at the time the investigation was done; therefore, information collected for quality improvement purposes would not be intended to contribute to generalizable knowledge even if it is later determined to be valuable and published or shared with others.

A number of WG members asserted that it is unclear whether product development contributes to generalizable knowledge or is considered for internal purposes only. WG members did not come to a consensus on whether intent to sell biobank data constitutes intent to contribute to generalizable knowledge. One WG member, using the All of Us Biospecimen Bank²¹ as an

²⁰ 45 C.F.R. § 46.116(e)(1), (f)(1).

²¹ The All of Us Research Program is an effort to have 1 million people in the US provide biospecimens in order to create the largest biological database in history. The Program is run by that National Institutes of Health and in partnership with the Mayo Clinic, maintains a biobank of blood, urine, and saliva samples for research purposes.

example, commented that biobanks could be considered research because, although the particular research project is unknown, the biobank is created with the intent that research will be performed in the future. However, others commented that this may be more like commercial entities, such as Facebook, which collect and sell personal data without publishing documents based on the data. Still, one WG member commented that health data could be different from the data typically sold by commercial entities in that it should be more protected. The Common Rule does not address selling data, but does require the company to indicate that results may be shared with others when obtaining broad consent. One WG member commented that, in his experience, patients who undergo DTC microbiome-based testing usually have not considered how their data may be used and are uncomfortable with the idea that they paid for test results which the company may sell and from which it may profit. Another WG member commented that it is difficult to make consumers aware of how their data may be used. Stronger regulation may be needed because consumers are unlikely to read Terms of Service agreements.

The working group discussed that Terms of Service like BIOHM's probably are not IRB approved. Although DTC microbiome-based testing companies may use the federal guidelines to draft their consent forms, they are not required to follow the regulations and obtain IRB approval unless they are taking federal grant funds or are seeking FDA approval for a product.²² A company may also need IRB approval if it is seeking to publish, since peer-reviewed publications often require a verification that the study was IRB approved. This is likely why BIOHM has a separate Consent to Participate in Research form that more closely follows informed consent requirements for research that it intends to publish.

WG members suggested that other companies may have Terms of Service that look different from BIOHM's. Some companies have a blanket statement that the customer's information may be used for research or improving the product. Some companies allow the customer to request that the sample be destroyed once testing is complete, while others do not. Additionally, some say that the Terms of Service may be changed at any time, which is concerning. One WG member commented that requiring a customer to agree to participate in the biobank to receive testing seems coercive.

The WG also discussed whether individuals should have ownership of their stool samples. One WG member suggested that samples like stool or blood are less "yours" or "part of you" than DNA samples because they are regenerative. However, some WG members disagreed with this proposition because regenerative samples contain human cells that could be sequenced to obtain identifiable information about a person's genome. Another WG participant stated that companies should be able to use the information obtained from samples so long as they are transparent and tell the consumer about such uses. This participant thought that restrictions on companies should be limited because important research and developments may not be possible otherwise. The new

Biobank, NAT'L INSTS. HEALTH, <https://allofus.nih.gov/funding-and-program-partners/biobank> (last visited Feb. 26, 2023).

²² In addition, individual states may require compliance with federal regulations for all research. For example, the Maryland Code states that "[a] person may not conduct research using a human subject unless the person conducts the research in accordance with the federal regulations on the protection of human subjects," and such regulations apply to all research regardless of any limits set forth in federal regulations. MD. CODE ANN., HEALTH-GEN. § 13-2002 (West 2022). States may also impose their own requirements for human subjects research. *See, e.g.*, VA. CODE ANN. § 13.1-162.16 et seq. (West 2022).

Common Rule’s adoption of broad consent reflects a movement to reduce restrictions on the use of information from large data sets.

Secondary Harms from DTC Microbiome-Based Testing

The next two presentations focused on secondary harms that might result from DTC microbiome-based tests. First, **Larry J. Forney, PhD, MS, University Distinguished Professor, Department of Biological Sciences, University of Idaho**, discussed how microbiome-based test results can be used to stigmatize individuals. Professor Forney asserted that there are false notions about what it means to have a healthy vagina, which lead women to feel shame and be stigmatized. There is a misconception that healthy women will have more or less the same vaginal microbiome composition. In reality, the vaginal microbiomes of healthy women may look vastly different, and the vaginal microbiome of even a single individual will fluctuate over time.

The most common condition associated with an “unhealthy” microbiome is bacterial vaginosis (BV). BV is associated with a number of increased risks, including pelvic inflammatory disease, acquisition of sexually transmitted infections; vaginal malodor; and, in obstetrics, preterm delivery and low birth weight, premature rupture of membranes, postpartum endometritis, and amniotic fluid infection. Given these risks, it is important for the diagnostic criteria for BV to be accurate. Currently, the clinical diagnosis of BV is based on the presence of three of the four following criteria: a vaginal pH of greater than 4.5; a thin, homogenous discharge; a positive “whiff” test or release of amine odor with the addition of a base; and clue cells on microscopic evaluation of wet mount.

Professor Forney introduced the idea of the “woozle” effect—a pattern of bias seen within science that leads to multiple errors in individual and public perception, academia, policy making, and government. “Woozles” occur when a claim lacks evidence but the public is misled and believes that the information is true because it continues to be repeated and cited in publications. The presence of a woozle makes it difficult to find accurate information and misleads the public, including health care providers and researchers, in ways that can be harmful.

There are four woozles about healthy vaginas. The first is that the vaginal communities of healthy women are dominated by species of *Lactobacillus*. While a number of studies have shown that women with high numbers of *Lactobacillus* species are healthy, it cannot be said that the opposite is true, i.e., that women whose vaginal communities have few or no *Lactobacillus* species are unhealthy. Yet, there is a common misconception that lack of *Lactobacillus* species is abnormal or unhealthy. In reality, a study of 396 women found that 27% of healthy women did not have a high proportion of *Lactobacillus*.²³ Women of one ethnic group may also have vaginal communities that differ from women of other ethnic groups; characterizing all women based on one or a few group’s most common microbiome might be damaging and add to negative stigma.

The second woozle is that the vaginas of healthy women are acidic with a pH of less than 4.5. Again, the opposite is not true, i.e., that a vaginal pH of greater than 4.5 is unhealthy. In a study

²³ Jacques Ravel et. al, *Vaginal Microbiome of Reproductive-age Women*, 108 PNAS 4680, 4681–82 (2011), <https://www.pnas.org/doi/epdf/10.1073/pnas.1002611107>.

of 89 asymptomatic women each sampled daily for 10 weeks, 48.3% of women had a median pH greater than 4.5.²⁴ The study found that pH varied within an individual woman over time, and also found there were differences in mean pH among ethnic groups. For Black and Hispanic women, the median pH was greater than 4.5.²⁵ Additionally, the 4.5 pH reference only refers to reproductive age women. For adolescents and postmenopausal women, the mean pH is 6.0 to 6.5.²⁶ Notably, the Human Microbiome Project²⁷ excluded participants who had a vaginal pH of greater than 4.5 because they were deemed “unhealthy.”²⁸ The potential exclusion of certain groups based on a false notion of what constitutes a healthy pH shows how these false notions of what is “normal” can be damaging.

The third woozle is that vaginal communities are reasonably stable, except perhaps during menstruation and disease. Studies have shown that vaginal communities do not remain stable; in the example provided in the presentation, the level of lactobacilli and *Gardnerella vaginalis* fluctuated over time.²⁹ It is not known why such fluctuations occur, but it is evident that fluctuations in vaginal communities occur in healthy women.

The final woozle is that the sole function of lactic acid in the vagina is to lower the environmental pH. Studies have found that lactic acid isomers differentially affect host gene expression and are modulated by environmental pH.

Understanding this information is not only important in properly diagnosing women, but is also important in reducing stigma. Women face stigma particularly around vaginal odor, even though there may be changes in odor with the normal fluctuation of vaginal microbiome composition. They may in turn seek remedies for a condition that is normal. Women who have been diagnosed with BV report feeling embarrassed, self-conscious, uncomfortable, ashamed, dirty, annoyed, and distressed.³⁰ They find it difficult to talk about BV because of the stigma around vaginal odor. Using words like “abnormal,” “not average,” “unbalanced,” and the like adds to the stigma, and may cause a person to make decisions about their health based on information that is not accurate. It is important to remember that even if 95% of healthy women share a similar vaginal

²⁴ These findings are from unpublished research by Larry Forney and Jacques Ravel.

²⁵ See also Jacques Ravel et. al, *Vaginal Microbiome of Reproductive-age Women*, 108 PNAS 4680, 4683 (2011), <https://www.pnas.org/doi/epdf/10.1073/pnas.1002611107> (finding a median pH of 5.0 in Hispanic women and a median pH of 4.7 in Black women).

²⁶ James C. Caillouette et al., *Vaginal pH as a Marker for Bacterial Pathogens and Menopausal Status*, 176 AM. J. OBSTETRICS & GYNECOLOGY 1270 (1997), [https://www.ajog.org/article/S0002-9378\(97\)70345-4/fulltext](https://www.ajog.org/article/S0002-9378(97)70345-4/fulltext).

²⁷ The Human Microbiome Project was a National Institutes of Health (NIH) funded research initiative that sought to characterize the composition of the human microbiome. NIH HUM. MICROBIOME PROJECT, <https://hmpdacc.org/> (last visited Feb 26, 2023).

²⁸ PAMELA MCINNES & MARY CUTTING., MANUAL OF PROCEDURES FOR HUMAN MICROBIOME PROJECT: CORE MICROBIOME SAMPLING PROTOCOL A HMP PROTOCOL # 07-001 at 6–10 (2010), https://www.hmpdacc.org/doc/HMP_MOP_Version12_0_072910.pdf (“If the mean pH at the posterior fornix is >4.5 at screening, the subject is not eligible for study enrollment.”).

²⁹ See Pawel Gajer et al., *Temporal Dynamics of the Human Vaginal Microbiota*, 4(132) SCI. TRANSLATIONAL MED. 132ra52, at 5 (2012), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3722878/>; Jacques Ravel et al., *Daily Temporal Dynamics of Vaginal Microbiota Before, During and After Episodes of Bacterial Vaginosis*, 1 MICROBIOME 29, at 3–4 (2013), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3968321/>.

³⁰ Jade E. Bilardi et al., *The Burden of Bacterial Vaginosis: Women’s Experience of the Physical, Emotional, Sexual and Social Impact of Living with Recurrent Bacterial Vaginosis*, 8 PLOS ONE e74378, at 4–9 (2013), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770676/pdf/pone.0074378.pdf>.

microbiome composition, 5% of healthy women will have a different microbiome. Although 5% may seem rare, 5% means 1 in 20 women will have a microbiome composition different than the majority while still being healthy.

Larry Forney's presentation may be found [here](#).

Next, **Jacques Ravel, PhD, MSc, Acting Director, Institute for Genome Sciences, University of Maryland School of Medicine**, discussed whether DTC microbiome-based test results could be used to identify an individual.

To determine that the microbiome can establish identity, it must be shown that (1) a “metagenomic code” that is specific to an individual in a sample population can be identified from the microbiome, (2) the code can be robustly re-detected at a later time, (3) the code is unlikely to erroneously match a previously unseen sample, and (4) the code can be constructed for a sizeable fraction of individuals, ideally the entire population.

One study found that individuals could be uniquely identified among populations of hundreds based on their microbiome alone.³¹ The study used metagenomic sequencing, a whole genome shotgun sequencing of a biological sample, on a variety of body site samples from the skin, oral, gut, and vaginal microbiomes. This technique sequences the genome of both the microbes contained and the human genome in the human cells present. The study found that the feasibility of identifying someone based on their microbiome is site-specific. Based on an averaging of all of the body sites tested, approximately one third of individuals could be precisely identified at a later time based on the species and mutations contained in the genome of their microbiomes. Testing the gut microbiome alone, greater than 80% of participants could be uniquely identified. This result raises potential privacy concerns for subjects enrolled in human microbiome research projects. One limitation of the study is that the population size was small, only in the hundreds. To be identifiable at the population level, one must guarantee that the match cannot be assigned to anybody else in the population. The study showed that identification by microbiome can lead to inclusion but not exclusion, i.e., an individual can be re-matched with their microbiome composition, but all other individuals cannot be excluded. Microbiome features are generally less unique and less stable than features of the human genome, meaning that the ability to identify individuals using their microbiome does not match the high specificity of the ability to identify individuals based on their genome.

Although there may be a need to regulate the identifying information in microbiome composition data, human genetic information remains the best and most reliable data to identify a person. However, human genetic information is virtually always co-generated along with microbiome genetic information in any metagenomic sequence when microbiome samples are analyzed. The amount of human genetic information in a sample varies based on the body site. For example, mucosal sites such as the vagina and oral cavity have more human genetic data, up to 95% of the sequenced data from these sites will be human rather than microbial. The human genetic information obtained can be used to identify an individual.

³¹ Eric A. Franzosa et al., *Identifying Personal Microbiomes Using Metagenomic Codes*, PNAS, May 11, 2015, at E2930, <https://www.pnas.org/doi/epdf/10.1073/pnas.1423854112>.

Human DNA sequences are routinely removed from microbiome datasets, at least in the research context. However, while it may be possible to separate human DNA from microbiome DNA prior to data generation, it is difficult to do without affecting the microbiome composition results. As a result, the data is usually removed after data generation. Based on a limited search of privacy statements from DTC microbiome-based testing companies using metagenomic sequencing, companies are not disclosing how sequenced human genetic information is being handled. If it is stored, it could potentially raise privacy issues.

The degree to which the human microbiome is identifiable is relevant to law enforcement use, forensic genetics, and genetic information privacy. Privacy concerns extend beyond merely identifying an individual; human genetic information is becoming increasingly powerful for subject characterization, including prediction of physical traits, disease risk, demography, and family history. Thus, the ability to obtain human genetic information from microbiome samples presents concerns, even if the microbiome itself is not as useful a tool as a genetic sample for identifying individuals.

Jacques Ravel's presentation may be found [here](#).

Discussion

Following the presentation, the WG discussed whether there might be other misuses of consumer data or harms to the consumer if information is distributed or disclosed to third parties without the consumer's consent.

WG members discussed the possibility that if microbiome composition can tell you about a person's habits, such as whether they have a poor diet, heavily drink, or smoke, the information could potentially be used by employers or insurers to deny or raise the price of insurance. Health insurance would not be affected due to the Affordable Care Act, but discriminatory decisions could still be made with respect to other benefits like life insurance, disability insurance, and long-term care insurance. Employers and insurers may gather this information by requiring certain testing of employees or applicants for insurance. For example, in the case of the "Devious Defecator," the employer required employees to undergo DNA testing to determine which employee was defecating in a company warehouse.³² Employers and insurers could also offer the test under the guise of a wellness initiative to improve lifestyle while covertly obtaining information that would allow the employer or insurer to identify those who pose medical risks. One WG member questioned whether it may be possible to gather data from employees unwittingly by collecting discarded waste, although she questioned whether the results would be useful given the poor quality of a discarded sample.

The WG discussed the possibility that if an individual's microbiome composition could show that they have traveled to a certain area, that information might be relevant for law enforcement or security clearance purposes. WG members, however, thought it would be difficult to discover that information through microbiome testing.

³² *Atlas Logistics Group Retail Services Atlanta, LLC*, 102 F. Supp. 3d 1360 (N.D. Ga. 2015).

Another WG member suggested that stigma associated with vaginal microbiome test results may cause women to make decisions about their reproductive lives that may be inaccurate. For example, if a certain microbiome were associated with infertility, women might make different decisions about marriage or family life than they would have otherwise.

The WG was not sure how probable these risks are, but one WG member pointed out that the technology is only going to improve. As the microbiome is better linked to behaviors, identity, or disease, the potential for harm becomes more likely.

Consumer Privacy and Third-Party Use of Data

Natalie Ram, JD, Professor of Law, University of Maryland Carey School of Law, gave the first presentation on the second day of the WG meeting. She discussed whether federal laws and constitutional protections currently in place to protect health information would apply to DTC microbiome-based tests. While these laws are currently used to protect genetic information for DTC genetic tests, the microbiome may be different and less of a privacy risk than genetic information for two reasons. First, as discussed by Jacques Ravel, the microbiome may not be as reliable and specific in identifying individuals as the human genome, although microbiome samples may contain human DNA that can lead to identification. Second, the microbiome may not have a familial aspect to it.³³ Human genetic information imposes troubling privacy risks in part because it can give law enforcement and others information about family members and familial relationships. The microbiome may be more like a fingerprint, where each person has a unique composition that is different from their family members, which would raise fewer privacy concerns.

Professor Ram first discussed the Health Insurance Portability and Accountability Act (HIPAA), passed by Congress in 1996. HIPAA protects individuals from the disclosure of their protected health information (PHI). Since the enactment of the Genetic Information Nondiscrimination Act (GINA) in 2008, PHI includes identified genetic data. Importantly, however, deidentified data and the biospecimens themselves are not considered PHI. The safe harbor provision for deidentified information outlines seventeen identifiers which, if removed, renders the information no longer PHI and no longer protected by the HIPAA privacy rule.³⁴ For genetic information, this is troublesome because even deidentified information can be reidentified relatively easily. As discussed earlier, the microbiome can potentially be reidentified with the individual, although not as reliably as human DNA. Still, the human DNA within microbiome samples may raise concerns.

³³ Some studies show that people's microbiomes tend to be more similar to their family members' microbiomes than to those outside of their family. See, e.g., Simon Lax et al., *Longitudinal Analysis of Microbial Interaction Between Humans and the Indoor Environment*, 345 SCIENCE 1048, at 3, 5 (2014), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4337996/pdf/nihms663075.pdf>. However, family members' microbiomes sometimes are not similar at all. *Id.* With respect to the vaginal microbiome, one study found that mother and daughter pairs have shared strains of bacteria. Michael T. France et al., *Identification of Shared Bacterial Strains in the Vaginal Microbiota of Related and Unrelated Reproductive-age Mothers and Daughters Using Genome-Resolved Metagenomics*, 17 PLOS ONE e0275908 (2022), <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0275908>. However, the same bacteria can also be found in completely unrelated women. *Id.*

³⁴ 45 C.F.R. § 164.514(b)(2).

Additionally, the HIPAA privacy rule only applies to covered entities and their business associates. A “covered entity” is defined under 45 C.F.R. § 160.103 to include health plans, health plan clearinghouses, and health care providers. That definition typically leaves out modern medical-adjacent consumer services; for example, the HIPAA privacy rule has not been applied to consumer genetics platforms. In fact, consumer genetics platforms often include language in their terms of service to make clear that they are not providing a medical service in an attempt to ensure they are not considered health care providers. Thus, it is likely that HIPAA’s privacy rule similarly will not apply to DTC microbiome-based testing companies. Additionally, a company will not be considered a business associate³⁵ unless the physician has a legal relationship with the company. For example, even if a physician handed their patient a test kit and instructed their patient to complete the test and return with the results, the testing company would not be a business associate because there is no legal relationship, such as a contract, between the covered entity and the company.

Even if the HIPAA privacy rule would otherwise apply, there are a number of exceptions that may subject the information to disclosure, for example, for law enforcement and public health purposes. These exceptions are often relatively broad. For example, law enforcement may be granted access to PHI through a court-ordered warrant, subpoena, or even a simpler administrative request.³⁶ Thus, even when HIPAA does apply, it is not the most robust protection.

GINA protects individuals from discrimination in health insurance and employment based on their genetic information. Note that this protection is limited to these two areas, and would not apply to other potential discrimination, like discrimination in decisions about life insurance, education, housing, law enforcement, etc. Genetic information is defined to include information about an individual’s genetic tests and the genetic tests and medical history of an individual’s family members. GINA typically applies to human DNA, so it is not evident that it would apply to microbiome-based testing. However, because human DNA is present in microbiome samples, there may be protection for at least some of the information obtained. For example, in *Lowe v. Atlas Logistics Group Retail Services Atlanta, LLC*³⁷ (AKA, the case of the “Devious Defecator”), an employer required two employees to submit genetic tests to match DNA samples to that of stool samples found in the employer’s warehouse. The employees sued, and the court sided with the employees. Even though the test was intended only to identify the person defecating in the warehouse and not intended to reveal medical information, the court held the employee’s genetic information is protected under GINA.

Certificates of confidentiality provide the strongest protections in federal law, protecting research findings from disclosure to law enforcement. Unlike HIPAA, certificates of confidentiality make

³⁵ Federal regulations define a business associate as a person that (1) “creates, receives, maintains, or transmits” PHI for covered entities, or (2) provides administrative services like consulting, data aggregation, accounting, management, etc. 45 C.F.R. § 160.103. The term includes (1) a “person that provides data transmission services with respect to [PHI]”, (2) “[a] person that offers a personal health record to one or more individuals on behalf of a covered entity,” and (3) “[a] subcontractor that creates, receives, maintains, or transmits [PHI] on behalf of the business associate.” *Id.*

³⁶ 45 C.F.R. § 164.512(f).

³⁷ 102 F. Supp. 3d 1360 (N.D. Ga. 2015).

the protected information immune from the legal process, so it cannot be accessed using court orders and the like. Also, unlike HIPAA, the protection continues for perpetuity and applies even if the information is transferred to a non-covered entity. Federally funded researchers developing or identifying sensitive information about subjects are required to obtain a certificate to receive grant funding. Non-federally funded researchers can also apply for a certificate. 42 U.S.C. § 241(d) says that anyone who has a certificate shall not disclose any identifiable sensitive information about individuals who contributed to the research. Identifiable sensitive information means information gathered about an individual during the course of research “through which an individual is identified” or “for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request of the information, and other available data sources could be used to deduce the identity of an individual.”³⁸ HHS has interpreted identifiable sensitive information broadly. Given the possibility that microbiome information can be used to identify individuals, certificates of confidentiality could potentially apply in this realm. However, certificates of confidentiality only apply as to information created or compiled for the purposes of research; commercial use of consumer information is not covered. Additionally, certificates are only required if federal funding is involved or the private researcher decides to apply for a certificate, and only apply to the extent that HHS recognizes that microbiome research produces identifiable sensitive information and requires a certificate.

Another possible protection of sensitive information is the Fourth Amendment. The Fourth Amendment protects against searches by the government or its agents without a warrant. A warrant is required to the extent there is a reasonable expectation of privacy in the thing being searched. Typically, things we throw away are considered abandoned, and along with them any reasonable expectation of privacy is abandoned, allowing the government to search without a warrant. Stool is inherently something that we throw away, so it is difficult to see how there is a reasonable expectation of privacy in it. However, there is an argument that although stool is discarded, that does not mean that the individual loses a reasonable expectation of privacy in the medically relevant information that may be obtained by analyzing the sample, which otherwise the individual would not voluntarily share. This argument has arisen in the context of waste water monitoring; a consumer’s act of sending their sample to a third party may or may not be analogous. While arguments are being made that the Fourth Amendment should shield consumer genetic data from certain kinds of law enforcement uses, part of that argument rests on the growing popularity of consumer genetic tests. As the microbiome testing market is much smaller, those arguments may be more difficult to make.

When federal statutes and constitutional protections don’t apply, we are left with industry self-regulation. It is unlikely that companies will provide the privacy protections that consumers need and want because the company’s incentives likely diverge from those of the consumer. Because companies can profit from consumer data, they will likely continue to do so if possible.

Additionally, as new uses of the information develop, companies may go through ownership changes where new owners seek to utilize consumer information in new ways. Consumers often do not understand the extent of, or lack of, privacy protections because they often do not read or understand the company’s terms of service. Even if they did, companies often reserve the right to make unilateral changes to the terms of service, so any protections provided may be gone in the

³⁸ 42 C.F.R. § 241(d)(4).

future. The FTC may bring an enforcement action if there is an egregious violation of the terms of service or privacy policy, but that would be rare.³⁹

Natalie Ram's PowerPoint presentation may be found [here](#).

Breakout Session #3

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

1. Based on the presentation and discussion yesterday, what secondary harms related to DTC microbiome-based tests do you think should be of concern for regulators? In light of those concerns, should vaginal and gut microbiome tests be regulated differently?
2. Should these tests be protected as personal health information (similar to protections provided under HIPAA)?
3. Should manufacturers be permitted to sell the data they collect from these tests to third parties without explicit consent from consumers? i.e., "Do you consent to the sale by X company of your microbiome data to third parties for research purposes? For marketing purposes?"
4. Should manufacturers be required to separate out customer DNA from their microbiome samples before providing them to third parties?
5. Are protections such as those provided by GINA necessary for DTC microbiome-based tests?

WG members discussed a range of secondary harms that could result from DTC microbiome-based testing. Consumers could suffer harm if their personal information is not protected, such as employment discrimination or stigmatization. Several groups mentioned that vaginal microbiome test results could reveal information about sexual practices, which could lead to stigmatization or even be dangerous in certain geographic areas. WG members continued to express concern about the harms when consumers, physicians, and other medical professionals like nutritionists act on the test results to change diet or treat disease. One WG member commented that the storage of this information is concerning because if there are security concerns and the company is hacked there could be many inadvertent disclosures.

WG members found it concerning that individuals could be identified based on the human genetic information present in the sample or unique microbiome of the individual. The WG felt that if it is possible to separate out human DNA from the microbiome sample, companies should be required to do so. However, it may be challenging or impractical to do so. If the company is sharing samples, it is probably impossible or unworkable to separate out the human DNA. However, companies can likely separate out human genetic data after analysis, and should be required to do so before sharing the compiled data. At present, companies are not required to filter out human genomic data, which is concerning if the data is then being sold or shared. It is

³⁹ The FTC did take enforcement action against a DTC genetic testing company, Genelink, Inc., for violating its privacy policy and misusing and failing to secure the personal information it collected. Complaint at 12–14, Genelink, Inc., No. C-4456 (Fed. Trade Comm'n May 12, 2014), <https://www.ftc.gov/system/files/documents/cases/140512genelinkcmpt.pdf>.

especially concerning if companies do not notify customers that human DNA could be detected and used from their microbiome samples, as patients may not be aware of this.

One breakout group expressed concern that law enforcement may be able to request a microbiome sample to obtain someone's genetic information. One WG member commented that once the government has access to your information, remedies may be difficult, because it is difficult to litigate with the federal government, which has unlimited funds. It is important that consumers understand the potential risk of having their genetic information compromised, but disclaimers in terms of service are often ineffective. One option would be to require companies to notify an individual if law enforcement requests their sample so that the person is on notice and can attempt to legally intervene.

The WG discussed the fact that some companies say they use an IRB, but that fact alone does not necessarily mean the company is engaging in ethical practices. If IRB review is not required, the IRB might legitimately review the privacy and ethics of the company's practices, but it is also possible that the IRB merely acts as a rubber stamp for the appearance of ethical practices.

WG members noted differences between vaginal and gut microbiome tests, like how much genetic information may be present in the sample and the stigma attached to the private information that may be revealed. However, many WG members agreed that the tests should be treated the same.

WG members felt that information obtained by microbiome-based tests should be protected as personal health information. Members noted that HIPAA is not a perfect framework. For example, HIPAA doesn't apply to deidentified data, and deidentified data is often used by DTC microbiome-based companies. WG members questioned whether removing the seventeen identifiers outlined in HIPAA regulations would actually deidentify the information, given the human genetic information present in the samples and potential uniqueness of the individual's microbiome. One breakout group found that some laboratories made statements that they were in compliance with HIPAA, and questioned whether laboratories made these statement for promotional purposes or because they are subject to HIPAA as covered entities or business associates.⁴⁰

WG members generally agreed that DTC microbiome-based testing companies should not be able to sell consumer's data, at least without explicit consumer consent. One group felt that an opt-in model for informed consent with robust, informative disclosures would be ideal. However, the group was unsure whether the FDA has jurisdiction to require such informed consent, since it does not necessarily speak to the safety or effectiveness of the test. Another group commented that consent may be meaningless if consumers do not read the company's terms and conditions.

⁴⁰ Microbiome laboratories providing DTC tests are not covered entities or business associates under HIPAA unless they provide test results to covered entities, i.e., providers, hospitals, or health insurers.

The background readings for the WG meeting included a consumer report outlining how genetic testing companies are engaging in data brokering and selling consumer information.⁴¹ The companies are not selling genetic information, but other data that might be supplied along with the sample such as health history, dietary habits, age, address, and even credit card information. It highlighted that companies were over-collecting non-genetic information and oversharing that information. WG members commented that DTC microbiome-based testing companies likely do the same thing. This problem is not unique to DTC testing, but something that exists in the entire digital ecosystem.

Some WG members commented that in the U.S. federal privacy protections are sectoral, meaning they provide protections for specific types of information. This results in gaps in privacy protections. While it would be useful to include microbiome information in our currently existing privacy laws, a comprehensive regime is likely needed to deal with digital information sharing in general. Some states are taking the lead on this issue. For example, Illinois has a Biometric Information Privacy Act, which resulted in a million-dollar judgement against an employer for collecting fingerprints from its workers.⁴² Maryland passed the nation's first comprehensive regulatory regime for law enforcement use of consumer genetics data in 2022.⁴³

The Future of Privacy Forum has published best practices for consumer genetic testing services,⁴⁴ which may be relevant in the DTC microbiome-based testing realm. It recommends banning the sharing of data with employers or insurance companies without consent, providing consumers with a way to delete genetic data stored with the company, requiring privacy commitments to stay the same if the company is bought, crafting more detailed consent forms for participating in research, allowing consumers to have control over which research their data will support, and requiring disclosure of all third parties with whom data will be shared. In addition, it advocates for prohibiting the use of consumer data for product development, or at least requiring explicit consent to use consumer data for such purposes.

One group commented that they felt consumers should have the option to ask the company to delete all their data and destroy their sample. However, they noted that CLIA labs must maintain all data for a minimum of seven years, so this would not be possible given that these labs are required to be CLIA certified.

WG members agreed, to the extent it was not currently covered, that it would be beneficial to expand GINA to include microbiome information. The microbiome could be used to discriminate against a person in employment. For example, if a food service employee's results showed they were colonized with *Salmonella*, an employment decision could be made against them. In the future, microbiome test results could show a predisposition to cancer or diabetes, which could be used to make adverse decisions against an individual in employment or health insurance. If microbiome information is not included, microbiome tests could be used as a work-

⁴¹ Catherine Roberts, *The Privacy Problems of Direct-to-Consumer Genetic Testing*, CONSUMER REPS. (Jan. 14, 2022), <https://www.consumerreports.org/dna-test-kits/privacy-and-direct-to-consumer-genetic-testing-dna-test-kits-a1187212155/>.

⁴² *Cothron v. White Castle Sys., Inc.*, 467 F. Supp. 3d 604 (N.D. Ill. 2020).

⁴³ MD. CODE ANN., COM. LAW §§ 14-4401 to -4408 (West 2022).

⁴⁴ Carson Martinez, *Privacy Best Practices for Consumer Genetic Testing Services*, FUTURE PRIV. F. (July 31, 2018), <https://fpf.org/blog/privacy-best-practices-for-consumer-genetic-testing-services/>.

around to GINA-protected information. Microbiome test results may provide some of the same information, like predisposition to disease, but while an employer could not require a genetic test, they currently could require a microbiome test. The WG did not see any downsides to including microbiome information under GINA. One WG member commented that GINA protections should be strengthened to make it harder for law enforcement to access data that is collected for health reasons.

State Regulation of DTC Microbiome-Based Testing

Jennifer Herbst, JD, LLM, MBIO, Professor of Law and Medical Sciences, Quinnipiac University School of Law, Frank H. Netter MD School of Medicine, discussed whether DTC microbiome-based tests can be regulated under state law as the practice of medicine or under the practice of another professional health occupation.

State law consists of civil, administrative, and criminal law.⁴⁵ While federal law also contains some civil law, civil claims tend to be more predominant at the state level. Malpractice, breach of contract, unfair trade practices, consumer privacy, and workplace discrimination claims are all civil law claims that may be available to redress harms caused by DTC microbiome-based tests. Civil law is generally driven by private individuals, although the government sometimes brings civil actions. Plaintiffs must show individualized harm to bring a civil action. In the DTC microbiome-based context, administrative law comes into play when medical boards and boards for other licensed professionals discipline practitioners for misconduct. Disciplinary actions are driven by both private individuals and government actors, with private actors bringing grievances and board members deciding whether to deny, restrict, suspend, or revoke professional licenses. Medical board disciplinary actions and licensing are tools for regulating physician practices that are unique to states and not available to the federal government. The unlicensed practice of a profession is often a criminal charge. Criminal law is driven by government actors, with attorney generals deciding when to sue based on their own preferences and public support for the particular action.

Whether DTC microbiome-based testing constitutes the practice of medicine depends on the law in each individual state. States differ in how they define the practice of medicine, but it generally includes elements of diagnosing, treating, operating, or prescribing. For example, Connecticut’s medical licensing law says that no person shall “diagnose, treat, operate for or prescribe for any injury, deformity, ailment or disease” without a license.⁴⁶ By contrast, Idaho defines the practice of medicine as the “investigation, diagnosis, treatment, correction, or prevention of or

⁴⁵ The enforcement action taken against uBiome is an example of how state law can be a tool to remedy harms caused by DTC microbiome-based tests. uBiome marketed “clinical” gut and vaginal microbiome tests and sought reimbursement from health insurance companies, including Medicare plans, for tests that were not medically necessary and not legitimately ordered by doctors. At the federal level, uBiome was charged with conspiracy to commit securities fraud and health care fraud, money laundering, and other related offenses. Press Release, uBiome Co-Founders Charged with Federal Securities, Health Care Fraud Conspiracies (March 18, 2021), <https://www.justice.gov/usao-ndca/pr/ubiome-co-founders-charged-federal-securities-health-care-fraud-conspiracies>. However, the California Department of Insurance and California Medical Board were also involved and did their own investigations of the matter. The Journal, *What Went Wrong at uBiome, Part 2*, WALL ST. J., at 17:06 (Nov. 12, 2021, 1:43 PM), <https://www.engadget.com/2019-04-28-ubiome-faces-fbi-investigation.html>.

⁴⁶ CONN. GEN. STAT. § 20-9(a).

prescription for any human disease . . . or other condition, physical or mental, by any means or instrumentality that involves the application of principles or techniques of medical science.”⁴⁷

Whether a recommendation related to diet might be considered “prescribing” depends on the jurisdiction and how they define and interpret their laws.

Depending on the claims about detecting or preventing disease and recommendations related to diet or supplements, there is at least an argument that some DTC microbiome-based testing companies are engaging in the practice of medicine.

Even if DTC microbiome-based testing companies are engaging in the practice of medicine, enforcement is not guaranteed. The steps to get from misconduct to disciplinary action can be seen in **Figure 3**.⁴⁸ Individuals cannot bring actions themselves but must file grievances with the medical board.

Whether a grievance is filed in the first place depends on whether the aggrieved party can recognize the harm and is motivated to take action. Whether there is harm may not always be clear, and opinions may differ on whether there is misconduct. The harms caused by DTC microbiome-based tests may not be evident to all. Sometimes competitors file grievances, although they are not aggrieved parties, to maintain market dominance.

When a grievance is filed, the medical board must decide whether it is worth pursuing. Whether a grievance is investigated will depend on whether the claim is substantiated and definite enough. Upon investigating the claim, there must be enough evidence to prove that there was misconduct. Once misconduct is proven, the board must decide whether to pursue minor or major disciplinary action. Whether disciplinary action is brought will differ by state depending on the make-up and priorities of the board. Typically, most medical board members are people licensed in the profession. These boards are interested in protecting their profession and protecting the public health in ways that judges would not be. One study found that there is a fourfold variation between states in the annual rate of medical board disciplinary actions taken

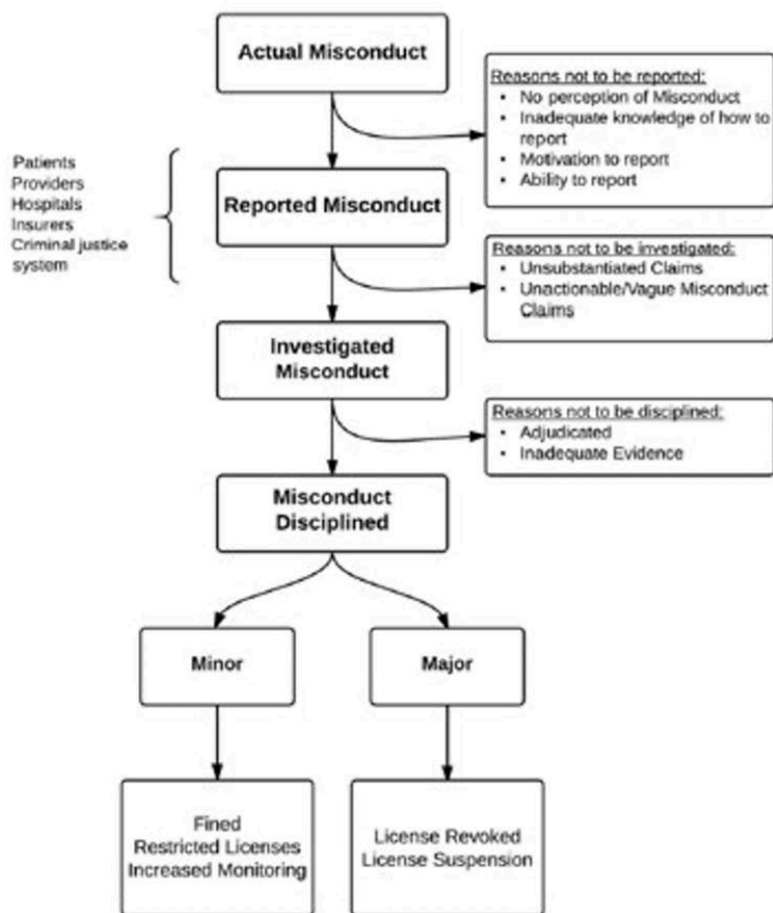


Figure 3. Steps from Misconduct to Disciplinary Action

⁴⁷ IDAHO CODE § 54-1803(1)(a).

⁴⁸ John Alexander Harris & Elena Byhoff, *Variations by State in Physician Disciplinary Actions by US Medical Licensure Boards*, 26 BMJ QUALITY & SAFETY 200 (2017), <https://pubmed.ncbi.nlm.nih.gov/27009311/>.

against physicians, exemplifying how enforcement differs greatly from state to state.⁴⁹

Another study analyzed what types of misconduct led to disciplinary actions within the American Medical Association.⁵⁰ The behaviors that led to disciplinary action the most often were controlled substance violations, substance abuse disorder, negligence and incompetence, criminal activity, and fraud or misrepresentation. For DTC microbiome-based tests, there could potentially be claims of fraud or misrepresentation, violating the terms of agreement, or perhaps unprofessional conduct. However, the misconduct physicians are typically disciplined for are not necessarily good matches for what DTC microbiome-based testing companies do. So, while DTC microbiome-based testing may constitute the practice of medicine, and claims alleging the unlicensed practice of medicine may be appropriate, it is harder to make claims alleging the type of misconduct that leads to disciplinary action.

Even if DTC microbiome-based tests do not constitute the practice of medicine, they could fall under the practice of another profession that may require licensure under state law—specifically, dietitians and nutritionists. **Figure 4** outlines the states with licensure for dietitians (with states requiring licensure in red),⁵¹ and **Figure 5** outlines the states with licensure for nutritionists (with states requiring licensure in red and yellow).⁵² These figures demonstrate that more states require licensure for dietitians than nutritionists.

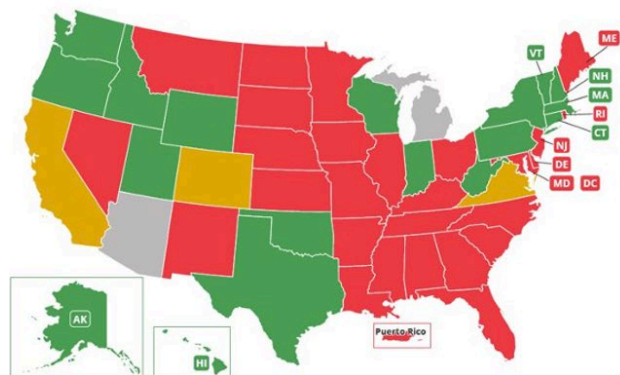


Figure 4. States Requiring Licensure of Dietitians

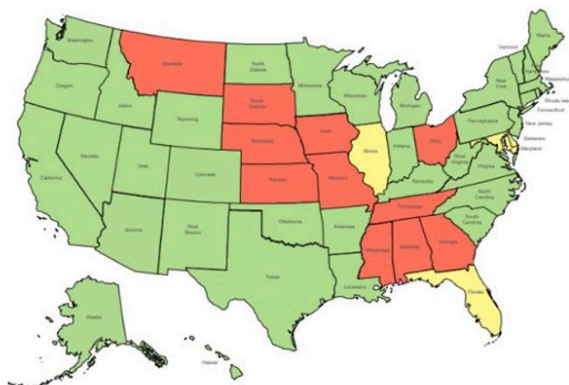


Figure 5. States Requiring Licensure for Nutritionists

According to the Academy of Nutrition and Dietetics, dietetics is “the integration, application and communication of practice principles derived from food, nutrition, social, business and basic

⁴⁹ *Id.*

⁵⁰ Kavita Shah Arora, Sharon Douglas & Susan Dorr Goold, *What Brings Physicians to Disciplinary Review? A Further Subcategorization*, 5 *AJOB EMPIRICAL BIOETHICS* 53 (2014), https://www.tandfonline.com/doi/pdf/10.1080/23294515.2014.920427?casa_token=fOo-g-IUki8AAAAA:qPgLpibQOPjG-tCGaBzqpWUufZKvu41LAYbTR_nPR7MiPljfNBCyNHpIS0ONPJA VngCr8k81y88.

⁵¹ *Licensure Map and Statutes by State*, EAT RIGHT PRO, <https://www.eatrightpro.org/advocacy/licensure/licensure-map-and-statutes-by-state> (last visited Feb. 4, 2023).

⁵² *State Regulation of Nutrition Practice*, AM. NUTRITION ASS’N, <https://www.theana.org/advocate> (last visited Feb. 4, 2023).

sciences, to achieve and maintain optimal nutrition status of individuals and groups.”⁵³ By contrast, nutrition is defined as the “science of food, the nutrients and other substances therein, their action, interaction and balance in relation to health and disease, and the process by which the organism ingests, absorbs, transports, utilizes and excretes food substances.”⁵⁴ Thus, nutrition is the science, while dietetics is the application of that science. The Academy says that “[a]ll registered dietitians are nutritionists, but not all nutritionists are registered dietitians.”⁵⁵ The terms Registered Dietitian (RD) and Registered Dietitian Nutritionist (RDN) refer to individuals who are credentialed in dietetics.⁵⁶ The Academy acknowledges that some states have licensure laws for nutritionists and dietitians, and directs its members to “[r]efer to state laws and licensure boards for each state’s specific licensing acts.”⁵⁷ Thus, the state law’s definition of nutritionist and dietetics will be the most helpful in determining the scope of practice and defining the two practice areas.

Maryland provides one example of a dietetics licensing law. Maryland defines the practice of dietetics to mean “apply[ing] the principles derived from integrating knowledge of food, biochemistry, physiology, management science, behavioral science, and social science to human nutrition.”⁵⁸ This includes [a]ssessing individuals and community food practices and nutritional status using anthropometric, biochemical, clinical, dietary, and demographic data, for clinical, research, and program planning purposes” and “[a]pplying scientific research to the role of food in the maintenance of health and treatment of disease.”⁵⁹ DTC microbiome-based tests that make diet recommendations could easily fit into this definition.

Maryland’s State Board of Dietetic Practice can deny a license, reprimand a licensee, or suspend or revoke a license if the applicant or licensee “[c]ommits fraud or deceit in the practice of dietetics . . . [u]ses or promotes or causes the use of any misleading, deceiving, or untruthful advertising matter . . . [p]ractices dietetics with an unauthorized person or supervises or aids an unauthorized person in the practice of dietetics . . . [or] [p]romotes the sale of devices, appliances, or goods to a patient so as to exploit the patient for financial gain.”⁶⁰ DTC microbiome-based testing companies’ practices of relying on tests that lack clinical validity, making recommendations based on information that is not scientifically proven, recommending diets without a licensed dietitian, and making recommendations for their own products could thus be cause for enforcement action.

Further bolstering the argument that DTC microbiome-based testing companies are practicing dietetics is that dietitians are increasingly identifying the microbiome as part of their practice. In its most recent standards of practice and standards of professional performance for Registered Dietitian Nutritionists, the Academy of Nutrition and Dietetics references the microbiome

⁵³ ACADEMY OF NUTRITION AND DIETETICS, ACADEMY OF NUTRITION AND DIETETICS DEFINITION OF TERMS LIST 28 (2021), <https://www.eatrightpro.org/-/media/files/eatrightpro/practice/academy-definition-of-terms-list-feb-2021.pdf>.

⁵⁴ *Id.* at 27.

⁵⁵ *Id.* at 2.

⁵⁶ *Id.*

⁵⁷ *Id.* at 47, 55.

⁵⁸ MD. CODE ANN., HEALTH OCC. § 5-101(h)(1).

⁵⁹ MD. CODE ANN., HEALTH OCC. § 5-101(h)(2).

⁶⁰ MD. CODE ANN., HEALTH OCC. § 5-311.

several times. It states that dietitians “demonstrate depth and breadth of knowledge in nutritional biochemistry, genomics, environmental toxicology, and *the microbiome*”; “[t]he patient-centered approach considers the interplay between a person’s genetic predispositions, *microbiome*, environmental inputs, and lifestyle”; dietitians use “information from ‘omic’ sciences (eg, genomics, proteomics, and metabolomics), environmental toxicology, and *microbiome-based research* to inform the assessment”; and “[a]ll areas are interconnected and influenced by a person’s biochemical and genetic uniqueness, illustrated by the DNA and *microbiota strands* linking the five key areas [of integrative and functional medical nutrition therapy].”⁶¹ The number of times that the term “microbiome” has been included in the Journal of the Academy of Nutrition and Dietetics has increased in the past ten years, amounting to 10-15% of the material in the journal. However, although the microbiome is described as key to what dietitians do, they recognize that “[m]ore research is needed before specific plant foods can be recommended to improve gut microbiota and ultimately health.”⁶²

This is a rare instance where the law may be ahead of the science. States are experimenting with laws regulating dietetics and nutritionists, which may provide a legal tool for addressing and regulating DTC microbiome-based testing. However, the patchwork of state laws can hinder innovation, as it is expensive to do legal research across all 50 states.

Jennifer Herbst’s PowerPoint presentation may be found [here](#).

Discussion

The WG discussed how the law of the state where the consumer is would likely apply to a DTC microbiome-based testing company because the state has an interest in keeping its residents safe from those practicing without a license. Personal jurisdiction jurisprudence says that there are sufficient contacts with the state to have jurisdiction when the company advertises to consumers in the state and has contact with the state. Regardless, state medical boards do not necessarily require strict jurisdictional components to act until the final agency action has been appealed and heard by the state court. This means that DTC microbiome-based testing companies who offer their tests in all 50 states would potentially need licensed providers in every state. DTC microbiome-based testing companies might achieve this result by having a network of licensed providers to match with consumers in each state. WG members also discussed that some states are adopting non-resident license policies to provide a streamlined process for providers in another state to obtain a license within the state. However, maintaining licenses in multiple states is very costly, so it would be impractical for a provider to become licensed in many states.

WG members commented that DTC microbiome-based testing companies often offer online consults. The state of telemedicine services is currently in flux after COVID. Legal prohibitions

⁶¹ Diana Noland & Sudha Raj, *Academy of Nutrition and Dietetics: Revised 2019 Standards of Practice and Standards of Professional Performance for Registered Dietitian Nutritionists (Competent, Proficient, and Expert) in Nutrition and Integrative and Functional Medicine*, 119 J. ACAD. NUTRITION & DIETETICS 1019, (2019), [https://www.jandonline.org/article/S2212-2672\(19\)30194-7/pdf](https://www.jandonline.org/article/S2212-2672(19)30194-7/pdf) (emphasis added).

⁶² Holly J. Willis & Joanne L. Slavin, *The Influence of Diet Interventions Using Whole, Plant Food on the Gut Microbiome: A Narrative Review*, 120 J. ACAD. NUTRITION & DIETETICS 608 (2020), https://www.sciencedirect.com/science/article/abs/pii/S2212267219313723?casa_token=GK1j16wGp50AAAAA:2dqwsEvXj9G9MM78yir5qxxD8eI9k8FR6EIOQM28TKm1fKWR4HlSt1lgX3iq7JWKEs_OafP.

on telemedicine services were waived during the public health emergency. Now that state and federal public health emergencies have ended, with the benefits of telemedicine better understood, it is unclear whether laws limiting telemedicine will continue to be enforced. Still, companies and health systems are implementing policies prohibiting telemedicine visits with patients out of state, concerned that telemedicine visits with out-of-state patients could give rise to disciplinary action or issues with health insurance reimbursement. One WG member commented that, in the medication therapy management space, some states are allowing out-of-state pharmacy benefit managers to provide in-state consultations if they register with the state.

Many WG members felt that the difference between a nutritionist and a dietitian is not clear. The distinction is important, however, because some states require a license for dietitians, but not nutritionists. These professions are relatively new, and the line of demarcation will be determined on a state-by-state basis. The recommendation of vitamins and supplements likely falls into the work done by dietitians and nutritionists. It is unclear whether dietitians are focused on the entire microbiome, including the microbiome of the skin and vagina, or only the gut microbiome.

Conclusion

Diane Hoffmann concluded the third and final WG meeting by thanking all those who participated. The next step in the process is to publish articles informed by the work done by the WG. WG members interested in publishing or finding co-authors should reach out to the co-investigators. WG members could set up additional virtual meetings as desired, or collaborate on curating a special issue of a journal focused on DTC microbiome-based testing.

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Appendix B Specific Controls for 23andMe Personal Genome Services

Table 1 – Identified Risks to Health and Identified Mitigations⁶³

Identified Risks to Health Identified	Mitigations
Incorrect understanding of the device and test system	General controls and special controls (1), (3), and (4)
Incorrect test results (false positives, false negatives)	General controls and special controls (2) and (3)
Incorrect interpretation of test results	General controls and special controls (1), (3), and (4)

In combination with the general controls of the FD&C Act, a genetic health risk assessment system is subject to the following special controls:

(1) The 21 CFR 809.10 compliant labeling and any prepurchase page and test report generated, unless otherwise specified, must include:

(i) A section addressed to users with the following information:

(A) The limiting statement explaining that this test provides genetic risk information based on assessment of specific genetic variants but does not report on a user’s entire genetic profile. This test [does not/may not, as appropriate] detect all genetic variants related to a given disease, and the absence of a variant tested does not rule out the presence of other genetic variants that may be related to the disease.

(B) The limiting statement explaining that other companies offering a genetic risk test may be detecting different genetic variants for the same disease, so the user may get different results using a test from a different company.

(C) The limiting statement explaining that other factors such as environmental and lifestyle risk factors may affect the risk of developing a given disease.

(D) The limiting statement explaining that some people may feel anxious about getting genetic test health results. This is normal. If the potential user feels very anxious, such user should speak to his or her doctor or other health care professional prior to collection of a sample for testing. This test is not a substitute for visits to a doctor or other health care professional. Users should consult with their doctor or other health care professional if they have any questions or concerns about the results of their test or their current state of health.

⁶³ Letter from Kelly Oliner for Lea Carrington, Director, Div. Immunology & Hematology Devices, U.S. Food & Drug Admin., to Lisa Charter, Director, Regul. Affs. & Quality Assurance, Dep’t Health & Hum. Servs. (Nov. 2, 2017), https://www.accessdata.fda.gov/cdrh_docs/pdf16/den160026.pdf.

(E) Information about how to obtain access to a genetic counselor, board-certified clinical molecular geneticist, or equivalent health care professional about the results of a user's test.

(F) The limiting statement explaining that this test is not intended to diagnose a disease, tell you anything about your current state of health, or be used to make medical decisions, including whether or not you should take a medication or how much of a medication you should take.

(G) A limiting statement explaining that the laboratory may not be able to process a sample, and a description of the next steps to be taken by the manufacturer and/or the customer, as applicable.

(ii) A section in your 21 CFR 809.10 labeling and any test report generated that is for health care professionals who may receive the test results from their patients with the following information:

(A) The limiting statement explaining that this test is not intended to diagnose a disease, determine medical treatment, or tell the user anything about their current state of health.

(B) The limiting statement explaining that this test is intended to provide users with their genetic information to inform lifestyle decisions and conversations with their doctor or other health care professional.

(C) The limiting statement explaining that any diagnostic or treatment decisions should be based on testing and/or other information that you determine to be appropriate for your patient.

(2) The genetic test must use a sample collection device that is FDA-cleared, -approved, or -classified as 510(k) exempt, with an indication for in vitro diagnostic use in over-the-counter DNA testing.

(3) The device's labeling must include a hyperlink to the manufacturer's public website where the manufacturer shall make the information identified in special control (3) publicly available. The manufacturer's home page, as well as the primary part of the manufacturer's website that discusses the device, must provide a hyperlink to the web page containing this information and must allow unrestricted viewing access. If the device can be purchased from the website or testing using the device can be ordered from the website, the same information must be found on the web page for ordering the device or provided in a publicly accessible hyperlink on the web page for ordering the device. Any changes to the device that could significantly affect safety or effectiveness would require new data or information in support of such changes, which would also have to be posted on the manufacturer's website. The information must include:

(ii) A section that highlights summary information that allows the user to understand how the

test works and how to interpret the results of the test. This section must, at a minimum, be written in plain language understandable to a lay user and include:

(A) Consistent explanations of the risk of disease associated with all variants included in the test. If there are different categories of risk, the manufacturer must provide literature references that support the different risk categories. If there will be multiple test reports and multiple variants, the risk categories must be defined similarly among them. For example, “increased risk” must be defined similarly between different test reports and different variant combinations.

(B) Clear context for the user to understand the context in which the cited clinical performance data support the risk reported. This includes, but is not limited to, any risks that are influenced by ethnicity, age, gender, environment, and lifestyle choices.

(C) Materials that explain the main concepts and terminology used in the test that include:

(1) Definitions: scientific terms that are used in the test reports.

(2) Prepurchase page: this page must contain information that informs the user about what information the test will provide. This includes, but is not limited to, variant information, the condition or disease associated with the variant(s), professional guideline recommendations for general genetic risk testing, the limitations associated with the test (e.g., test does not detect all variants related to the disease) and any precautionary information about the test the user should be aware of before purchase. When the test reports the risk of a life-threatening or irreversibly debilitating disease or condition for which there are few or no options to prevent, treat, or cure the disease, a user opt-in section must be provided. This opt-in page must be provided for each disease that falls into this category and must provide specific information relevant to each test result. The opt-in page must include:

(i) An option to accept or decline to receive this specific test result;

(ii) Specification of the risk involved if the user is found to have the specific genetic test result;

(iii) Professional guidelines that recommend when genetic testing for the associated target condition is or is not recommended; and

(iv) A recommendation to speak with a health care professional, genetic counselor, or equivalent professional before getting the results of the test.

(3) Frequently asked questions (FAQ) page: this page must provide information that is specific for each variant/disease pair that is reported. Information provided in this section must be scientifically valid and supported by corresponding publications. The FAQ page must explain the health condition/disease being tested, the purpose of the test, the information the test will and will not provide, the relevance of race and ethnicity to the test results, information about the population to which the variants in the test is most applicable, the meaning of the result(s), other risk factors that contribute to disease, appropriate follow up procedures, how the results of the test may affect the user's family, including children, and links to resources that provide additional information.

(iii) A technical information section containing the following information:

(D) Assay steps and technology used.

(F) Specification of the specimen collection, processing, storage, and preparation methods.

(H) Information pertaining to the probability of test failure (i.e., percentage of tests that failed quality control) based on data from clinical samples, a description of scenarios in which a test can fail (i.e., low sample volume, low DNA concentration, etc.), how users will be notified of a test failure, and the nature of follow up actions on a failed test to be taken by the user and the manufacturer.

(I) Specification of the criteria for test result interpretation and reporting.

(J) Information that demonstrates the performance characteristics of the test, including:

(1) Accuracy of study results for each claimed specimen type.

(i) Accuracy of the test shall be evaluated with fresh clinical specimens collected and processed in a manner consistent with the test's instructions for use. If this is impractical, fresh clinical samples may be substituted or supplemented with archived clinical samples. Archived samples shall have been collected previously in accordance with the instructions for use, stored appropriately, and randomly selected.

(ii) Accuracy must be evaluated by comparison to bidirectional Sanger sequencing or other methods identified as appropriate by FDA. Performance criteria for both the comparator method and the device must be predefined and appropriate to the device's intended use. Detailed study protocols must be provided.

(2) Precision and reproducibility data must be provided using multiple instruments and multiple operators, on multiple non-consecutive days, and

using multiple reagent lots. The sample panel must either include specimens from the claimed sample type (e.g., saliva) representing all genotypes for each variant (e.g., wild type, heterozygous, and homozygous) or, if an alternative panel composition of specimens is identified by FDA as appropriate, a panel composed of those specimens FDA identified as appropriate. . .

(3) Analytical specificity data: data must be provided that evaluates the effect of potential endogenous and exogenous interferents on test performance, including specimen extraction and variant detection. Interferents tested must include those reasonably likely to be potentially relevant to the sample type used for the device. (4) Interfering variant data: nucleotide mutations that can interfere with the technology must be cited and evaluated.

(5) Analytical sensitivity data: data must be provided demonstrating the minimum amount of ___ that will enable the test to perform correctly in 95 percent of runs.

(K) Clinical performance summary.

(1) Information to support the clinical performance of each variant reported by the test must be provided. (2) Manufacturers must organize information by the specific variant combination as appropriate (e.g., wild type, heterozygous, homozygous, compound heterozygous, hemizygous genotypes). For each variant combination, information must be provided in the clinical performance section to support clinical performance for the risk category (e.g., not at risk, increased risk)

(M) User comprehension study: information on a study that assesses comprehension of the test process and results by potential users of the test must be provided.

(1) The intended use of the device must not include the following indications for use:

- (i) Prenatal testing;
- (ii) Determining predisposition for cancer where the result of the test may lead to prophylactic screening, confirmatory procedures, or treatments that may incur morbidity or mortality to the patient;
- (iii) Assessing the presence of genetic variants that impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications;