PERSONALIZED MEDICINE COALITION

July 12, 2019

Jeffrey Shuren, M.D., J.D.
Director, Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20857

Sent electronically

Re: Docket No. FDA-2019-N-1619: List of Patient Preference-Sensitive Priorities; Establishment of a Public Docket; Requests for Comments

Dear Dr. Shuren:

The Personalized Medicine Coalition (PMC), a multi-stakeholder group comprising more than 230 institutions and individuals across the health care spectrum, appreciates the opportunity to submit comments on the Center for Devices and Radiological Health (CDRH)'s *List of Patient Preference-Sensitive Priorities* as part of its initiative to incorporate patient preference information into regulatory decision-making. [i] We commend CDRH for developing a broad list of patient preference-sensitive topics[ii] for stakeholders to consider, and we applaud the center's goal of further incorporating the patient voice into medical device development.

Overall, PMC supports the direction of the priority list for its potential to bring personalized medicine closer to patients, but as the center proceeds with this initiative, we respectfully ask CDRH to include aspects of patients' values and circumstances as factors in decision-making; to consider uncertainties in the regulatory landscape for diagnostics; and to account for complexities in how patients evaluate the benefits and risks of direct-to-consumer genetic health tests and respond to subsequent information about genetic risk.

Personalized medicine is an evolving field that uses diagnostic tools to identify specific biological markers, often genetic, to help determine which medical interventions and procedures will be best for each patient. By combining this information with an individual's medical history, circumstances, and values, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans.

Identifying the benefits and risks of medical products that matter to patients is essential to the effective delivery of personalized medicine, which, as described, is defined not just by a patient's biology but also the individual's preferences. The priority list of patient preference-sensitive

areas developed by the agency as part of the Medical Device User Fee Amendments IV (MDUFA IV) agreement[iii] has the potential to advance activities that highlight the value patients place on the benefits and risks of a medical product, such as a diagnostic test kit. Such activities have the potential to impact the design and conduct of premarket clinical studies, benefit-risk assessments, and post-market evaluation of medical devices.

Statement of Neutrality

Many of PMC's members will present their own responses to FDA and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance, and are not intended to impact adversely the ability of individual PMC members, alone or in combination, to pursue separate comments on the *List of Patient Preference-Sensitive Priorities* or associated documents. Additionally, PMC does not hold a position on whether laboratory-developed tests (LDTs) should be regulated by the FDA or through the Clinical Laboratory Improvement Amendments (CLIA) program at the Centers for Medicare and Medicaid Services (CMS).

I.) Patient values and circumstances in diagnosis and treatment

Through an engagement award from the Patient-Centered Outcomes Research Institute (PCORI), PMC is convening patients, caregivers, health professionals, and other stakeholders to develop a research agenda for outcomes in personalized medicine that matter most to patients.[iv] Several conversations have led to the following preliminary definitions for patient values and patient circumstances when deciding on a personalized treatment.

- ***Patient/caregiver values*** *include personal priorities, religious/spiritual values, societal and cultural values (including family involvement in care decisions), views around quality of life, and beliefs about health and personal responsibility.*

- ***Patient/caregiver circumstances*** *include emotional state, socio-economic situation, race/ethnicity, language, ability to work, access to care, social support, cognitive abilities, attitude toward illness, personality, symptom burden, health-related quality of life, ability to consent and choose, relationship with the health care provider, the role of patient as a caretaker, and other expressed needs or barriers.*

Participants in the project have raised both "values" and "circumstances" as factors that should be weighted equally with a patient's biology in treatment decision-making. CDRH's priority list highlights the ranking of factors in decision-making as a patient preference-sensitive priority area. PMC suggests that CDRH consider the criteria identified through PMC's PCORI project as additional factors in decision-making.

II.) Complexities in the diagnostics landscape

Diagnostic test kits that provide genetic information or molecular profiles on patients are essential to

personalized medicine. The proposed list breaks out diagnostic and genetic testing as separate medical specialties, and we support CDRH's incorporation of patient preferences into regulatory decision-making in these areas when it is appropriate and possible. As CDRH considers how to achieve the incorporation of patient preference information into its work now and in the future, PMC would like to highlight uncertainties that may present future challenges.

Legislative efforts, such as the proposed "Verifying Accurate Leading-edge IVCT Development Act of 2018," seek to clarify oversight of diagnostic tests and, if enacted, have the potential to create a new regulatory paradigm. PMC encourages CDRH to maintain flexibility in application of this priority list in order to accommodate any new regulatory paradigm impacting pre- and post-market review.

III.) Complexities in direct-to-consumer (DTC) genetic testing

PMC recognizes the ability of direct-to-consumer (DTC) genetic health test results to inform personalized medicine.

DTC genetic health tests provide information on disease risk indicators, pharmacogenomic or drug metabolism indicators, and carrier status indicators. Results from these different tests may inform a patient about the comparative risks of getting certain health conditions, the way the patient may react to some medications and dosages, and the potential for the patient to pass on a gene that can impact the patient's children's chances of developing certain genetic diseases or conditions.[v] PMC suggests CDRH consider patients' preferences related to health information for these different purposes.

Further, we share concerns that patients as consumers do not all understand the level of risk associated with different genetic markers included within DTC genetic health test results; when to involve a physician; and how to respond to the results from a DTC test. A complete grasp of these issues requires a patient to have an accurate understanding of the varying levels of accuracy, reliability and usefulness of tests; the importance of repeat or confirmatory testing; the difference between tests providing information about genetic risk, or susceptibility to developing a disease or condition, versus diagnosis; whether or not medical interventions are available; and nuances in legal and privacy protections. As a result, a consumer may misinterpret their risk of developing a disease or condition and opt to either forgo necessary preventive measures or pursue unnecessary medical interventions. Some information may be especially sensitive, and a patient should consider "opting out" of receiving results for certain diseases for which there are limited treatments or preventive interventions available. If a patient has questions or concerns about the implications of learning information from a DTC genetic health test, they should involve a health professional, such as a genetic counselor or physician well-versed in this area, who can help them respond appropriately to their genetic information.

PMC recently released a *Consumer's Guide to Genetic Health Testing*[vi] that includes a set of questions patients should ask before ordering a DTC genetic health test. We encourage CDRH to incorporate these questions, which are also presented as an appendix to this letter, into its evaluation of patient preferences for DTC genetic health tests.

IV.) Uncertainties related to secondary prevention of disease

The ability to predict and prevent the onset of disease through genetic information is a key benefit of personalized medicine.[vii] An added benefit is the ability to identify strategies that may reduce the impact of a disease that has already occurred. However, for some diseases, knowledge of genetic risk may create challenges for patients and their families when interventions to halt symptoms of the disease are insufficient and treatments to stop disease progression do not exist.

For Alzheimer's disease, genetic tests are available to report to consumers on the status of their Apolipoprotein-E ε4, or APOEε4, allele. Possession of one APOEε4 allele increases the risk of developing late onset Alzheimer's disease by 3- to 5-fold, and possession of two APOEε4 alleles increases risk 15 to 20-fold.[viii] With the rise of DTC genetic health tests, more consumers are offered information on their APOE status. The Alzheimer's Foundation of America (AFA) has call[ed] on researchers

> *to revisit past analysis of APOE genetic disclosure and conduct new research on how such information can influence both positive and negative outcomes, including lifestyle changes and future planning steps as well as stress, depression, anxiety, suicidal ideation, and suicide among individuals to whom this information is disclosed.*[ix]

PMC would support CDRH's consideration of a proposal like this into the center's efforts to account for patient preferences in the secondary prevention of disease. We believe a research framework similar to AFA's for evaluating the impact of uncertainty in the secondary prevention of disease may also apply to other disease areas.

V.) Implementing the proposed list

Given the breadth of the topics proposed, PMC suggests that CDRH consider the relative complexity of incorporating patient preferences into regulatory considerations for diagnostic and genetic testing against other areas identified on the priority list and focus on the most straightforward items first. PMC believes that further stakeholder engagement on complicated patient preference-sensitive areas like diagnostics and genetic testing is warranted to provide direction to CDRH on how to prioritize activities that incorporate patient preference information in a manner that addresses patients' most immediate needs.

Conclusion

Thank you for considering our comments. PMC welcomes the opportunity to serve as a resource to the agency as this list of patient preference-sensitive priorities is refined. If you have any questions about the content of this letter, please contact David Davenport, PMC's Manager, Public Policy & Secretary to the Board, at 202-787-5913 or ddavenport@personalizedmedicinecoalition.org.

Sincerely,

Cynthia A. Bens
Senior Vice President, Public Policy

CC: Anindita Saha
Director, External Expertise and Partnerships
Office of Center Director, Center for Devices and Radiological Health
Food and Drug Administration

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[i] Food and Drug Administration. *List of Patient Preference-Sensitive Priorities; Establishment of a Public Docket; Request for Comments*. May 3, 2019. https://www.regulations.gov/document?D=FDA-2019-N-1619-0001 Last accessed: July 3, 2019.
[ii] Center for Devices and Radiological Health. *Priority List of Patient Preference-Sensitive Areas*. May 2, 2019. https://www.fda.gov/about-fda/cdrh-patient-engagement/priority-list-patient-preference-sensitive-areas Last accessed: July 3, 2019.
[iii] Food and Drug Administration. *MDUFA IV Performance Goals and Procedures, Fiscal Years 2018 through 2022*. December 2, 2016. https://www.fda.gov/media/102699/download Last accessed: July 3, 2019.
[iv] Personalized Medicine Coalition. *Moving Beyond Population Averages: Patient Principles for a Personalized Medicine Research Agenda*. http://www.personalizedmedicinecoalition.org/Research/Moving_Beyond_Population_Averages_Patient_Principles_for_a_Personalized_Medicine_Research_Agenda Last accessed: July 3, 2019.
[v] Personalized Medicine Coalition. *A Consumer's Guide to Genetic Health Testing.* http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/A_Consumers_Guide_to_Genetic_Testing.pdf Last accessed: July 3, 2019.
[vi] Ibid. v.
[vii] Personalized Medicine Coalition. *The Personalized Medicine Report: Opportunity, Challenges, and the Future*. 2017. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The_PM_Report.pdf Last accessed: July 3, 2019.
[viii] Alzheimer's Foundation of America. *Statement of the Alzheimer's Foundation of America (AFA) and AFA's Medical, Scientific and Memory Screening Advisory Board on Genetic Testing to Determine Risk of Alzheimer's Disease.* https://alzfdn.org/genetesting/
[ix] Ibid. vii

Appendix:

Questions to Ask Related to Ordering a Direct-to-Consumer Genetic Health Test

Before deciding to order a genetic test:

1. What is my motivation for testing?
2. What information do I hope to get and how would I use this information?
3. Are the conditions being tested for important to me?
4. Will the test results offer peace of mind or increase stress and anxiety?
5. Will the test results help me make better health choices?
6. Are there actions I can take to improve my health based on the test results?
7. Does the vendor provide information I can use to help prevent disease after testing?
8. Will I have access to updates on discoveries and new information?
9. Will my results be kept private?
10. What are the implications of the results to my family and/or for family planning?
11. Is the test covered by my insurance policy?

After deciding to order a genetic test:

12. Are the genetic health tests offered by the vendor authorized by the FDA for over-the-counter use, or do they need to be prescribed by an authorized physician?
13. If the test is not cleared by FDA for over-the-counter use, does the vendor provide access to appropriately trained health care professionals, such as the prescribing physician, a certified genetic counselor, a clinical pathologist, or a clinical geneticist?
14. Does the vendor provide information about the test's accuracy, the laboratory's methods, and how it develops its test results?
15. Do the vendor's methods for performing genetic testing and generating results ensure high-quality and clinically relevant information?
16. Does the vendor take steps to confirm the accuracy of medically actionable results prior to adding them to your report?

Source: Personalized Medicine Coalition. *A Consumer's Guide to Genetic Health Testing.* http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/A_Consumers_Guide_to_Genetic_Testing.pdf Last accessed: July 3, 2019.