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Society for Functional Precision Medicine

Anthony G. Letai, M.D., Ph.D.
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September 1, 2022

Chiquita Brooks-LaSure, Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Attention: CMS–1751–P
Mail Stop C4–26–05
7500 Security Boulevard
Baltimore, MD 21244–1850

Dear Administrator Brooks-LaSure,

We, the board members of the Society for Functional Precision Medicine (SFPM), are writing to urge the retirement of policy NCD190.7, pertaining to the non-coverage of human tumor drug sensitivity assays. The SFPM is an international organization that includes academic and commercial members, joined by a common interest in supporting the rapidly advancing field of functional precision medicine with the scope of facilitating predictive assays to add to the standard clinical care of oncology patients. Our organization most commonly defines functional precision medicine in oncology as exposing viable patient tumor samples to therapeutics to determine whether a clinical response to said therapeutics could be observed. As such, we anticipate that the language of NCD190.7 might overlap with the approaches we refer to, and we are concerned that the assays of our members will be deemed not coverable without due consideration based on this rule alone.

We feel that there are several reasons why NCD190.7 should be retired. This is a rule that was initiated twenty-five years ago, and which has not been reviewed to our knowledge since the year 2000. We understand that two decades ago the performance of the specific tests evaluated and evidence for clinical benefit, while promising, was rightfully deemed insufficient to support CMS funding. However, since that time there have been major improvements in 1) the technologies and methods used to isolate, grow and study patient cancer cells *ex vivo* 2) the number of effective oncology drugs that belong to several different classes and have diverse mechanisms of action and most importantly 3) the level of formal clinical trial evidence validating the clinical benefit of FPM assays for specific cancer indications. Thus, the assays currently used today for patient care are vastly more informative and compelling compared to those which were in use 25 years ago.

Regarding the first point, in the intervening decades, technologies to better isolate, grow, maintain tumor cells ex vivo and approaches to thoroughly quality control such cultures have proliferated. This is a point

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highlighted by the recent NCI sponsored Human Cancer Models Initiative which has rapidly aided in the development of *ex vivo* culture methods to support next generation patient-derived cancer models. These advances include innovative three-dimensional culture techniques, such as an entire novel discipline of study of patient tumor spheroids and organoids. Two decades of extensive experimentation has led to an array of greatly improved culture conditions and substrates for two-dimensional and three-dimensional cultures. Tumor cells survive far better in these systems than 20 years ago, and are now proven to match the genomic and phenotypic characteristics of the patient tumor. Common problems of 20 years ago, such as overgrowth of non-malignant cells, have largely been solved.

In contrast with the year 2000, we have vastly superior methods of evaluating the effects of drugs on cancer cells. Two decades ago, techniques to study single cells were extremely limited, so that the drug sensitivity tests of those times relied nearly exclusively on average proliferation readouts that were subject to confounding effects unrelated to drug treatment. Moreover, there was no ability to discriminate the specific effects on tumor cells from the effects on non-tumor normal cells of the microenvironment, the latter of which often dominated ex vivo culture response readouts. Currently, there exist a far wider and more specific scope of assays available. Some study individual cell mass, some study specific apoptosis signaling at the single cell level, some study specific cell morphologies informed by extensive training of artificial intelligence algorithms. Techniques of cellular analysis that have revolutionized cancer biology research in the past two decades have now translated into a paradigm shift in the clinical diagnostic arena. It should be noted that this field and technologies are also expected to rapidly expand and so the current assays are just the beginning of a revolution in diagnostics.

Finally, the number of therapeutic agents approved by the FDA and available to cancer patients today has increased well over ten-fold in the intervening two decades. In 2000, even an assay with perfect sensitivity would have been able to provide information of only modest clinical utility since the choices were so meager. Today, there are hundreds of drugs approved by the FDA for the treatment of cancers, greatly increasing the utility of functional precision medicine assays that can accurately choose and prioritize treatment. As noted in prior CMS reviews of the approaches, the assays have dual benefit in that they can both identify effective agents as well as help patients and payors avoid costly yet ineffective treatments. The functional precision medicine technologies allow patients and providers to take advantage of individualized data which, while complementary to other biomarkers current used as standard of care, can uniquely provide the most direct information of relevance to a provider and patient: the personalized response of their tumor cells to agents planned to be administered to them.

For these reasons, we believe that the blanket determination, heretofore provided by NCD190.7, that all assays in the general category of functional precision medicine are subject to non-coverage by CMS is

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therefore outdated and warrants consideration for revision or retirement. Today, there are over a dozen companies and tens of academic labs with functional precision medicine platform technologies in the United States alone, and many more internationally. The evidence supporting the utility of these assays greatly exceeds that available for the relatively primitive assays of 2000. Progress in this vital area of patient diagnostics, which pursues the fundamental task of identifying active drugs for cancer patients, will be impeded if providers of these assays, both commercial and academic, cannot seek reimbursement for their performance. The exciting advances in this area are therefore now feasible to aid patients but their wider and equitable accessibility is hampered by lack of CMS coverage.

If NCD190.7 were retired, we would suggest that an alternative would be to review functional precision assays instead under Medicare Administrative Contractor (MAC) discretion. Absent this change, we are very concerned that cancer patients will be unable to access the benefits of the modern functional precision medicine technologies that are poised to change how we choose drugs for individual patients. We hope retirement of NCD190.7 will therefore receive due consideration.

Sincerely,

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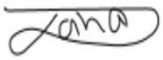

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