Association for Molecular Pathology
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Steven Teutsch, MD, MPH, SACGHS Chair
Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD, 20892

RE: Comments of The Association for Molecular Pathology to The Secretary's Advisory Committee on Genetics, Health and Society, June 15-16, 2010

Dear Dr. Teutsch:

The Association for Molecular Pathology (AMP) commends the Secretary's Advisory Committee for focusing on whole genome sequencing, an area of growing interest to the Association. Sequencing technology is advancing at a rapid pace with not only the cost and turn around time of processing a single sample dramatically decreasing but also the idea of sequencing an individual's entire genome moving from feasibility to reality. In time, as costs and turnaround times decrease further, whole genome sequencing technology will make targeted molecular tests less cost effective. It is reasonable to foresee whole genome sequencing techniques in a clinical laboratory and by extension, the clinic, in the next five years, and as such, AMP commends the Committee for investing time to explore and address the related challenges of policy and practice issues.

As the technology advances, AMP's concerns focus on the clinical applications of whole genome sequencing. The advent or adoption of the technology itself is not controversial, but how clinical laboratories apply the technology and physicians utilize the information to inform clinical decision -making can generate many ethical challenges and laboratory practice questions.

On a broad level, currently marketed molecular diagnostic tests encounter reimbursement and coverage hurdles. The current state of the art may consider whole genome sequencing as a screening test, placing it into a category with additional obstacles to adequate coverage and reimbursement by public and private payers. As all testing technology advances, AMP believes that reimbursement policies should be modernized to appropriately represent the value of the information obtained from laboratory tests that utilize whole genome analysis (or next-generation sequencing) techniques.

The wealth of data obtained in whole genome sequencing creates new practice questions that molecular pathologists will have to address. AMP believes that the cornerstone of integrating this technology into laboratory practice will be the assessment of its clinical utility. How can three billion base pairs of sequence and identification of the sequence of ~20,000 genes be

coupled to clinical utility? The answer to this rhetorical question is that there will be difficulty for molecular pathologists to associate meaning with the data generated by these tests and there will be further challenges to define a normal genome. An effective approach to this central question will depend upon a multi-disciplinary research agenda, which is critical to enabling accurate diagnostic interpretations. Also, there should be a central repository to submit clinical and analytical data of these analyses to further inform the interpretation and clinical utility of results.

Moreover, the vast amounts of data will require investments in bioinformatics technology not only to analyze, manage and store the data, but also to enable secure access to the data in a useful manner. Measures to standardize the data for entry into interoperable electronic medical records and to simplify the reporting of sequencing results will be required to ensure responsible adoption and implementation of this technology.

When healthcare providers request whole genome sequencing for a patient, they may indicate or describe a phenotype and/or symptoms. AMP is concerned that this poses an ethical quandary when molecular pathologists have access to the entire genome data set, but the provider is only interested in the interpretation for a specific indication. AMP members question whether it is responsible and appropriate to only report based on the test indication or whether there is a duty to report all findings regardless of the initial clinical indication for the test. In these instances, AMP members will need to consider whether they should mask the non-relevant data and only report based on the test requisition. Additionally, they will consider whether to then report data as new evidence as additional gene-disease associations become available. AMP encourages the Committee to consider the complicated ethical issues associated with the duty to report all data, update interpretations as new evidence emerges, and the appropriateness of masking data irrelevant to the test prescriber's indication.

AMP has provided comments to the Committee in the past on the issue of DNA patents, and has been pleased with the Committee's report and recommendations on this business practice. As whole genome sequencing becomes more widely used in the clinical setting, DNA patents on specific sequences may restrict the reporting and interpreting of the full results of such testing. This links to our concerns about clinical utility and the duty to report all results, and AMP fears laboratories performing whole genome sequencing will face infringement liability or risk incomplete reporting of clinically significant data.

Confounding these ethical issues are the anticipated communication gaps among the laboratories, physicians and patients. Molecular pathologists will have the added responsibility of educating the healthcare providers who request whole genome sequencing about the complexities of genetic associations, risk information and laboaratory decisions about which data to report and in what manner. These healthcare providers will, in turn, have the challenge of communicating the significance of this information to patients. With other areas of genomic medicine, AMP has recommended that the Committee continue to explore the provider education and training needs associated with implementing whole genome sequencing techniques into the clinical setting. AMP is aware that the Committee has released its draft report on the education and training of health care professionals, and we intend to submit comments later this month.

AMP wishes to clarify that next-generation sequencing techniques used in a laboratory-developed test or in a test submitted to the FDA for approval for the purpose of interrogating a

specific gene or condition should not be viewed as whole-genome methods even though the same technology approach may be used. A specific application using next-generation sequencing technology, versus whole genome screening, is simply "another laboratory test" using evolving technology, but used in a targeted manner and subject to all the same appropriate validation as any other molecular diagnostic test.

Lastly, AMP values the role of whole genome sequencing in characterizing the full genome of tumor samples. AMP members recognize that to truly capture the genomic changes associated with cancer, the results must be compared and contrasted with the patient's germline genome from, normal tissue, perhaps adjacent to the tumor or from a blood sample . Similar to our previous concerns, molecular pathologists will have the responsibility of determining what, if any, information about the patient's germline genome should be shared with the patient. The Committee and the sequencing community will need to address the ethical challenges associated with reporting large data sets before the technology is disseminated widely in the clinical setting, contributing to the promise of individualized disease prevention, detection, subtyping, prognostication, treatment and monitoring.

AMP thanks the Committee for focusing its attention on whole genome sequencing and looks forward to partnering with the Committee to explore these challenging issues that we have outlined today. To that end, AMP has formed a Working Group on Whole Genome Analysis. Thank you very much for your attention.

Sincerely,

Karen P. Mann, MD, PhD
President