# Association for Molecular Pathology

***Promoting Clinical Practice, Translational Research, and Education in Molecular Pathology***

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Amy Gutmann, Ph.D.
Chair, Presidential Commission for the Study of Bioethical Issues
1425 New York Avenue NW, Suite C-100
Washington, D.C. 20005
Sent electronically to info@bioethics.gov

Dear Dr. Gutmann,

Thank you for the opportunity to submit public comments on the ethical, legal, and social issues raised by incidental findings that arise from genetic and genomic testing. The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,000 pathologists and other laboratory medicine professionals who perform or are involved with clinical molecular diagnostic laboratory testing based on knowledge derived from molecular biology, genetics, genomics, and pathology. Membership includes professionals from the government, academic medicine and the in vitro diagnostics industry.

AMP members are at the frontlines of integrating genome-wide sequencing technologies into medical practice and research, and understand the challenges of reporting incidental findings for use in clinical settings. Nearly ten clinical laboratories in the United States now offer whole exome or whole genome sequencing. Therefore, the development of guidelines and standards for reporting incidental findings that arise during these procedures is needed. AMP is pleased that the Presidential Commission for the Study of Bioethical Issues (the Commission) is exploring the ethical, legal, and social issues related to large-scale genetic testing. In addition to the included comments **AMP offers its expertise as you further consider these issues beyond the current comment period. AMP members are available to review draft reports and recommendations, and to assist in any manner in which we can contribute to the Commission's efforts.**

The challenge of reporting incidental findings is not novel in medicine. With the advent of new imaging technologies such as MRI and CT scans, radiologists have already faced similar challenges and put forth practice guidelines to deal with what is often referred to as incidentalomas.[1] Although there are analogies between incidental findings in radiology and genomics, there are also important differences. In contrast to the descriptive reporting of a suspicious radiographic finding identified on visual inspection, reporting of incidental variants detected during genetic testing frequently requires substantial additional effort to evaluate such variants for their potential pathogenicity. Such investigations often involve extensive searches of medical literature and variant databases, as well as the application of computerized prediction programs to predict the functional consequences of a given genetic change. Reporting tends to be probabilistic in approach. Moreover, the downstream effects of incidental findings on radiographic and genomic examinations are likely to differ. Incidental findings in radiology often directly lead to invasive procedures that may have significant risks of morbidity or even mortality. By contrast, incidental findings in genetics appear more likely to result in actions such as monitoring, additional laboratory testing, and genetic testing of relatives, with potential harms largely psychological and economic as opposed to physical. Thus, although much can probably be learned from the radiology experience in addressing incidental findings, because of the aforementioned differences between radiology and genomics, **AMP encourages the Commission to review guidelines and consensus statements from professional societies of specialties such as pathology and genetics that are engaged in the practice of genomic medicine.**

For example, the American College of Medical Genetics (ACMG) recently published recommendations for reporting incidental findings from large-scale genetic testing in clinical settings. ACMG proposed a list of greater

[1] Berland et al. "Managing Incidental Findings on Abdominal CT: White Paper of the ACR Incidental Findings Committee." Journal of American Radiology 2010;7:754-773

than 50 genes, pathogenic variants in which should be reported to patients.[2] Medical actionability, the ability of providers to intervene to prevent or alter the course of a disease or syndrome, formed the basis for the ACMG recommendation. Our experience at AMP suggests that incidental findings are common in large-scale genetic testing. For example, one AMP member reviewed 50 random patients on whom whole exome sequencing had been performed, and found that approximately 20% had reportable incidental findings as defined by the ACMG guidelines. Because all of our genomes contain genomic variants of known and unknown significance, less stringent reporting criteria would result in an expanded number of reportable incidental findings. The definition of incidental finding and the criteria used to establish reportability will heavily influence the frequency with which incidental findings are released to patients and their providers, and the ratio of potential benefits to harms arising from the testing. **AMP encourages the Commission to collaborate with AMP and other professional societies to: clearly define what constitutes an incidental finding; set forth the process by which incidental findings should be searched for, identified, evaluated, confirmed, and their significance validated prior to reporting; provide guidance on the appropriateness of reporting sequence variants of various categories to patients; and establish standards for addressing incidental findings in minors, especially those variants causally implicated in adult onset diseases.**

**First and foremost, AMP believes that care should be taken to ensure that clinical approaches to whole genome sequencing are always centered on the patient's interests and well-being.** Specifically, all patients should be provided with genetic counseling before testing and at the time results are presented to them. Informed consent must be obtained prior to performing whole genome sequencing. Patient autonomy demands that informed patients decide whether or not to undergo whole genome or exome sequencing or other large-scale genetic testing, and have the right to prospectively determine the information that will be revealed to them. Prior to testing, patients should be informed that testing may identify incidental findings that may indicate susceptibility to diseases or disorders for which there may or may not be effective medical interventions or treatments. **AMP believes that an "opt in" form of consent,** in which patients select the genetic information they want revealed to them prior to testing, may best serve patients by preventing the communication of unwanted results, and preserving access to disease-related information a patient chooses to receive.

**AMP believes that patients have a right to learn information about their risks for untreatable diseases. Moreover, this information may inform personal decisions including, for example, those related to employment, the purchase of long term care insurance, or reproduction.** Some patients will derive emotional benefits from learning this health information, or experience emotional harms when it is withheld. These reasons all favor the right of patients to learn of pathogenic variants associated with disease processes for which there are no therapies.

Greater societal resources should be directed toward ensuring the provision of adequate pre- and post-test counseling for patients undergoing large-scale genetic testing. Patients need access to qualified healthcare professionals capable of discussing test results. Treating physicians and other healthcare providers need well developed consensus statements and guidelines on which they can rely, and the healthcare system needs resources to support proper follow up with appropriate specialists to address incidental findings. Resources must be dedicated to the creation, development and maintenance of centralized, curated databases of genomic variants, to which all laboratories should be strongly encouraged to submit de-identified data, including individual variants identified, relevant associated clinical information, and acquired information regarding potential pathogenicity. Data must be submitted with appropriate safeguards to protect patient privacy. Resources should be provided to allow for continual updating of the information contained within the database in order to ensure accurate and timely classification of variants. **AMP encourages the administration to invest in building this infrastructure including supporting efforts to expand the genomic medicine workforce (e.g., pathologists, medical geneticists, genetic counselors, etc.).**

**AMP believes genetic testing is best pursued in a medical setting in which pre-test and post-test genetic counseling are available. The likelihood of incidental findings and the reporting dilemmas they entail presents yet another argument in support of this position, and argues against the advisability of direct-to-**

[2] Green et al. "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing." Genetics in Medicine June 20, 2013

**consumer large-scale genetic testing.** Because the context, environment, and patient resources involved in performing direct-to-consumer genetic testing differ substantially from those associated with the traditional model of medically directed genetic testing, AMP urges the Commission to develop separate and distinct recommendations relating to incidental findings discovered in these two settings. Such recommendations should incorporate an understanding of the relative availability and provision of associated medical resources that these very different models of testing imply, as well as differences in their relative potential patient benefits and harms.

Our understanding of the human genome is constantly expanding and we urge the Commission to review and update its recommendations periodically to keep pace with scientific discovery and knowledge concerning the medical interpretation of genomic variants. Further study on the impact of these findings on patients and laboratory practices for reporting them is warranted, and will help inform future recommendations as well. Thank you again for the opportunity to submit these comments. **AMP looks forward to continuing this dialogue with the Commission on the reporting of incidental findings.** If you have any questions or AMP may be of further assistance, please contact Roger D. Klein, MD, JD, Chair, Professional Relations Committee at roger.klein@aya.yale.edu and Mary Williams, Executive Director, at mwilliams@amp.org or 301-634-7921.

Sincerely,

Jennifer L. Hunt, MD, MEd
President