REPORT 3 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-16)
The Precision Medicine Initiative
(Reference Committee E)

## EXECUTIVE SUMMARY

Objectives. "Precision medicine" is defined as prevention and treatment that takes into account individual variations in genes, environment, and lifestyle. In 2015, President Obama announced the Precision Medicine Initiative (PMI), an ambitious project with two overarching goals: intensified efforts toward the molecular characterization of cancers and development of targeted therapeutics; and the creation of a research cohort of over one million volunteers who will share genetic data, biological samples, and diet and lifestyle information, all linked to their electronic health records if they choose. The Council on Science and Public Health has initiated this report to inform physicians and the House of Delegates about the PMI and the potential ways that it could affect their practice and their patients.

Data Sources. Literature searches were conducted in the PubMed database for English-language articles published between 2010 and 2016 using the search terms "precision medicine initiative" and "precision medicine." These searches were intended to identify the impetus for the Precision Medicine Initiative and the reactions to it. To capture reports not indexed on PubMed, a Google search was conducted using the same search terms. Websites on the Precision Medicine Initiative, maintained by the White House, NIH, and NCI were consulted, as were reports by the Advisory Committee to the Director of the NIH and the Secretary's Advisory Committee on Genetics, Health, and Society. Additional articles were identified by manual review of the references cited in these publications.

Results. Implementation of the PMI is in the early stages, but a roadmap of key activities is emerging. The National Cancer Institute (NCI) plans to address obstacles that are commonly encountered in "precision oncology," e.g., unexplained drug resistance, genomic heterogeneity of tumors, insufficient means for monitoring responses and tumor recurrence, and limited knowledge about the use of drug combinations. The NIH plans to build a research cohort made up of more than one million individuals willing to provide access to their specimens and medical information and the collection of information about their environmental exposures (including physical, social, and behavioral information). The scale of the initiative means that physicians are likely to have clinical encounters with participants, and could view and use their patients' genomic and other health data to inform ongoing care. They may also have the opportunity to recruit patients to become part of the cohort, and may be asked by patients about cohort enrollment and health data sharing. In the near future, successful PMI research projects that are translated into clinic practice will result in additional genomic and digital data that could influence patient management.

Conclusions. The PMI is an ambitious initiative that holds great promise for improving patient care and outcomes. It will require the coordination and commitment of both the federal and private sectors, and rests on the interest and willingness of participants to enroll and share their health data. Ensuring that physicians are well-informed about the PMI, and have the educational and health IT resources needed for such an endeavor is vitally important. The Council believes that the AMA is well-positioned to improve awareness of the PMI among physicians and to act as a resource for physicians who have questions about how it will impact their patients.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 3-A-16

Subject: The Precision Medicine Initiative

Presented by: Louis J. Kraus, MD, Chair

Referred to: Reference Committee E
(Theodore Zanker, MD, Chair)

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BACKGROUND

During the 2015 State of the Union address, the President announced the Precision Medicine Initiative (PMI), an ambitious project aiming to "bring us closer to curing diseases like cancer and diabetes and give all of us access to the personalized information we need to keep ourselves and our families healthier."[1] The PMI has two overarching goals: intensified efforts toward the molecular characterization of cancers and development of targeted therapeutics; and the creation of a research cohort of over one million volunteers who will share genetic data, biological samples, and diet and lifestyle information, all linked to their electronic health records if they choose.[2] The Administration has tasked the National Institutes of Health (NIH), the National Cancer Institute (NCI), the Food and Drug Administration (FDA), and the Office of the National Coordinator for Health Information Technology (ONC) with carrying out various aspects of the PMI, and also has challenged private sector groups to assist in PMI efforts.[3]

In the context of the PMI, "precision medicine" is defined as prevention and treatment that takes into account individual variations in genes, environment, and lifestyle.[2] In some ways, physicians already are practicing "precision medicine" by managing each patient according to his or her unique symptoms, medical and family history, and preferences. However, recent technological advances such as the development of large-scale biologic databases (for example, the human genome sequence), powerful methods for characterizing patients (proteomics, metabolomics, genomics, cellular assays, and mobile health technologies), and computational tools for analyzing large sets of data have vastly improved the ability to apply precision medicine principles to patient care.[4]

Implementation of the PMI is in the early stages, but a roadmap of key activities is emerging. However, it is not yet clear how physicians will be affected by the PMI in the long term, and how they can contribute to its goals. The scale of the initiative, especially its goal of developing a large research cohort, means that physicians are likely to have clinical encounters with participants, and could view and use their patients' genomic and other health data to inform ongoing care. They could also have the opportunity to recruit patients to become part of the cohort, and may be asked by patients about cohort enrollment and health data sharing. In the near future, successful PMI research projects that are translated into clinic practice will result in additional genomic and digital data that could influence patient management. The Council on Science and Public Health has



Action of the AMA House of Delegates 2016 Annual Meeting: Council on Science and Public Health Report 3 Recommendations Adopted, and Remainder of Report Filed.

initiated this report to inform physicians and the House of Delegates about the PMI and the potential ways that it could affect their practice and their patients.

## METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2010 and 2016 using the search terms "precision medicine initiative" and "precision medicine." These searches were intended to identify the impetus for the Precision Medicine Initiative and the reactions to it. To capture reports not indexed on PubMed, a Google search was conducted using the same search terms. Websites on the Precision Medicine Initiative, maintained by the White House, NIH, and NCI were consulted, as were reports by the Advisory Committee to the Director of the NIH and the Secretary's Advisory Committee on Genetics, Health, and Society. Additional articles were identified by manual review of the references cited in these publications.

## OBJECTIVES OF THE PMI

### *More and better treatments for cancer*

The field of oncology is already making great strides in precision medicine. Risk assessment, diagnosis, prognosis and management can be tailored based on the genetic variations present in cancer cells. It has become standard practice to use multi-variant panel tests to determine risk of recurrence and magnitude of benefit of chemotherapy for certain breast cancers,[5] and a number of similar multi-variant panels exist for characterizing other tumor types.[6] Similarly, the availability and use of targeted therapeutics has increased. Nearly 50 oncology therapeutics targeted to genetic variations have been approved by the FDA.[7,8] However, too often, after remarkable results with a targeted therapeutic, cancer cells acquire resistance and stop responding. A deeper understanding of the molecular underpinnings of cancer is needed to develop more effective treatments, making the field of oncology a fitting candidate for the PMI.

The NCI has been tasked by the PMI with addressing obstacles that are commonly encountered in "precision oncology," e.g., unexplained drug resistance, genomic heterogeneity of tumors, insufficient means for monitoring responses and tumor recurrence, and limited knowledge about the use of drug combinations.[4] The NCI plans to address these obstacles by expanding precision medicine clinical trials focused on assigning patients to therapy targeted to the genetic alterations thought to be driving their cancer.[9] An example of this type of trial already underway is NCI-MATCH, a large, multi-site trial that analyzes patients' tumors to determine whether they contain genetic abnormalities for which a targeted drug already exists and assigns treatment based on the abnormality.[10] A pediatric version of NCI-MATCH is expected to launch in 2016.[11] Under the PMI, the NCI also plans to increase its support of research on the development of new *in vitro* models of human cancers and better understand what drives the molecular response to immunotherapies; and establish a "knowledge network," i.e., a national database that houses and integrates genomic information from tumors, including clinical response data and outcomes information, as a resource for scientists, health care professionals, and patients.[9]

### *Creation of a voluntary national research cohort*

For more than a decade, a case has been made for the development of a large U.S. research cohort, which would enable prospective studies on a wide range of diseases.[12-15] A research cohort is made up of a large number of individuals willing to provide access to their specimens and medical information and the collection of information about their environmental exposures (including physical, social, and behavioral information).[14] Data stored in databases and specimens stored in

repositories could then be accessed by qualified investigators for specific and approved research purposes.[14] Large research cohorts have been created recently by several groups, the largest of which include the U.S. Department of Veterans Affairs' Million Veteran Program; Geisinger Health System's MyCode Project; and Kaiser Permanente's Research Program on Genes, Environment, and Health.

As part of the PMI, the NIH has been tasked with creating a national research cohort. During much of 2015, a Working Group of the Advisory Committee to the Director of the NIH held public forums, solicited feedback, and developed plans around such issues as the unique scientific opportunities offered by the cohort, characteristics of already existing cohorts, effective mechanisms for analyzing large amounts of data, maximizing participant engagement, and using mobile and personal health technologies for data collection.[16] The Working Group issued a report late in 2015 with its recommendations for creating the cohort.[17] Among the recommendations were:

- Cohort Assembly: The PMI cohort should be a new, broadly accessible, national research resource of volunteers that reflect the diversity of the U.S. All potential participants in the cohort must agree to share their health data, provide a biospecimen (blood), and be recontacted for future research.
- Cohort Recruitment: Any individual living in America should have the opportunity to directly volunteer for the PMI Cohort Program or join through health care provider organizations (HPOs).
- Participant Engagement: The PMI Cohort Program should return to each participant their own results and aggregated results from its studies. Participants should be able to set preferences to dictate how much personal information they receive, and be able to change their preferences throughout their participation in the cohort.
- Data Collection and Storage: The PMI Cohort Program should anticipate and collect a diverse set of data types, beginning with a core set of high-value variables to be acquired during enrollment from all participants and stored centrally. The initial core data set should include data from electronic health records (EHRs), health insurance organizations, participant surveys, mHealth technologies, and biologic investigations.
- Data Security and Access: A data access control approach appropriate to the level of sensitivity of the data, from open-access for summary data to role-based access for individual level data, should be instituted. Data should be accessed and analyzed in de-identified forms, and secure computing environments should be used for data access and analysis.

## INITATIVES ENABLING THE PMI

To enable the PMI to proceed as the President has envisioned it, several improvements to research, regulatory, and data access infrastructures need to be instituted. Additionally, the innovative capabilities of private entities should be explored and applied to the PMI to solve current challenges.

### *Regulatory modernization*

The Common Rule. The collection and use of data that straddle the research and patient care boundary, such as that likely to be generated in the PMI, should be subject to principles that both protect the participants and foster innovation.[17] To that end, United States Department of Health and Human Services (HHS) announced late in 2015 proposed revisions to the Common Rule, the regulations governing the ethical conduct of research involving humans.[18,19] The revisions have two

central goals: enhance respect and safeguards for research participants, and increase research efficiency by reducing unnecessary burdens and calibrating oversight to the level of risk. A major step toward the latter goal was taken in February 2016 when the NIH announced that it is establishing a central PMI Cohort Program Institutional Review Board with expertise in mobile health technologies, bioinformatics, health disparities, epidemiology, genomics, and environmental health for oversight and review of the research conducted in the Cohort Program.[20]

Next-generation sequencing. As part of the PMI, the FDA has begun to explore what type of oversight framework and resources would be appropriate for the clinical tests used to analyze the biological information provided by participants.[21] Specifically, the FDA is focusing on the use of next-generation sequencing (NGS)-based technologies. NGS is a method for rapid and large-scale genomic sequencing; it is used in whole genome and whole exome sequencing, and often in panel-based tests that analyze dozens or even hundreds of genetic variants simultaneously.[22,23] NGS is distinct from narrowly targeted tests because it is likely to reveal a large number of secondary findings, i.e., genetic variants not related to the phenotype under investigation but that might impact a patient's health.[24] Since the biospecimens contributed to the PMI will likely be genetically analyzed using NGS-based testing, the FDA has been exploring oversight mechanisms for it. The FDA has stated that because NGS tests are capable of detecting so many genetic variants that were not necessarily the initial targets of the tests, the traditional construct of evaluating the safety and efficacy of a targeted test that detects only one or a few variants may not be applicable to NGS.[21,25]

The AMA has been active in its advocacy for genetic test oversight, including for NGS-based tests. The AMA supports a Clinical Laboratory Improvement Amendments (CLIA)-based laboratory oversight system along with appropriate third-party accreditation, and is opposed to FDA oversight of laboratory-developed testing services in all but the most narrow of circumstances.[26] Accordingly, the AMA has made public comments and statements for the record opposing FDA oversight that infringes on the practice of medicine, and has engaged with a broad group of stakeholders to support regulatory reform for genetic tests that promotes innovation and preserves patient access.[27-29]

Patient access to health data. The PMI has emphasized that the participants who volunteer to take part in the cohort will be treated as partners, including having access to the health data generated as a function of their participation. This includes returning personal results and information to individual participants and sharing aggregate findings from PMI investigations, and giving participants the opportunity to set preferences, and change those preferences at any time, to dictate how much personal health information they want to receive.[17]

Key to patient accessibility of health data generated in the PMI is the right of individuals to access and obtain a copy of their protected health information (PHI). In July of 2015, ONC and the Office for Civil Rights (OCR) announced they would work to address barriers that prevent patients from accessing their health data.[30] To honor that pledge, OCR in January 2016 issued guidance on the Health Insurance Portability and Accountability Act's provisions providing individuals with the right to access and receive a copy of their PHI held by healthcare providers and health plans.[31] Additional efforts toward patient access to health information by improving interoperability and accessibility have been undertaken by health technology stakeholders, including the AMA. In February 2016, the AMA, along with dozens of health information technology developers, healthcare systems and physician health provider advocacy groups, pledged to work with HHS to improve the flow of electronic health information to patients and physicians to increase data sharing.[32,33]

*Public-private partnerships*

The PMI will rely on partnerships with existing research cohorts, patient groups, and the private sector to develop the infrastructure that will be needed to expand the cancer genomics projects and to launch the Cohort Program.[3] In February 2016, the Administration announced grant awards to several private sector and federal entities to begin implementation of the Cohort Program. Grants were awarded to Vanderbilt University and Verily (formerly Google Life Sciences) to develop a direct-volunteer pilot program that will explore the optimal approaches and systems for engaging, enrolling, and retaining participants; the Health Resources and Services Administration to begin partnerships with Federally Qualified Health Centers to develop, pilot, and refine approaches for bringing underserved individuals, families, and communities into the PMI Cohort Program; and ONC for a program called "Sync for Science" ("S4S"), which will pilot use of open, standardized applications to give individuals the ability to contribute their data to research.[20]

Additionally, the Administration announced the commitments of more than 40 private sector organizations, including the AMA, health information technology companies, academic medical centers, biotechnology and pharmaceutical companies, research institutes, and advocacy groups, to assist in laying the foundation for the PMI, including patient access to their health data, engaging research participants as partners, improving data sharing, developing data security and privacy principles, and applying precision medicine to clinical practice.[34] The commitment of the AMA is:

> The AMA commits to actively working in 2016 to improve patient access to their medical information and helping physicians leverage electronic tools to make health information more readily available, developing and disseminating a range of resources including toolkits, podcasts, and fact sheets. The AMA will also improve awareness of the Precision Medicine Initiative among physicians, including: creating articles in AMA digital publications; educational sessions at AMA meetings; emails/posts/tweets through social media channels; and information about the Precision Medicine Initiative Cohort and how to volunteer, once enrollment begins.

## PHYSICIAN INVOLVEMENT IN COHORT PROGRAM RECRUITMENT

Currently, little is known about how physicians will be affected by the PMI, but the implementation plans announced for the Cohort Program suggest that physicians will play a key role in recruiting participants.

### *HPO participant recruitment*

One of the two methods of recruiting participants for the Cohort Program will be through health care provider organizations (HPOs), which the PMI defines as institutions at which patients receive care over time resulting in a longitudinal record of care available in electronic format with ongoing, documented follow-up.[17] Examples of HPOs include academic medical centers, Federally Qualified Health Centers, vertically integrated private health care organizations (e.g., Kaiser Permanente), and vertically integrated governmental organizations (e.g., VA).[17] Accordingly, physicians practicing at these institutions likely will be expected to talk with their patients about the Cohort Program and should be prepared to answer patients' questions about it. Topics may range from broad questions about what the Cohort Program is and what its goals are, to more specific questions about what type of information might be returned from the Cohort Program and how physicians might use it for patient management.

A baseline health exam and submission of a biospecimen (blood) will be required for participants; therefore physicians or their health professional team members will likely be performing the exams

and collecting the biospecimens. Even if the exams are conducted by a separate entity within the HPO, the data from the exam will be deposited into the patient's EHR and will be viewable and actionable by the patient's physician. Participants also are expected to share with the PMI certain health information in their EHR. Physicians therefore may need to be prepared to talk with their patients about health data sharing, security, and privacy. When participants receive individual results from the PMI, physicians should be prepared to answer patients' questions about what the results mean and how they could or should be applied to their care.

*Direct volunteer enrollment*

For those wishing to participate in the Cohort Program who do not have the opportunity to enroll through an HPO, a second mechanism for enrollment is through direct volunteerism.[17] These participants could be recruited through a number of technologies, such as Internet, social media, and mobile technologies, and through community and advocacy organizations and events. Participants volunteering must visit a health professional for a baseline exam and submission of a biospecimen. Physicians conducting these exams should be prepared to answer questions as discussed above, i.e., what the Cohort Program is and what its goals are; what type of information might be returned and how it might be applied to care; and what type of data sharing, security, and privacy protections are in place.

Participants volunteering outside of an HPO also must agree to share EHR data if they have it. The PMI envisions participants sharing their EHR using "Blue Button" technology, a term referring to patient online access to health care data with download ability and in some cases, transmittal to a third party application or service of the patient's choice.[17,35] Although this technology is not part of all EHR systems to date, public and private sector organizations have committed to make health information more easily available electronically to individuals and to encourage its use.[36] Physicians and their health professional team members may therefore be asked specifically about how to access and share health data from their EHR.

## CHALLENGES AND UNANSWERED QUESTIONS FOR PHYSICIANS

*Physician education about precision medicine and the PMI*

Successful PMI research projects that are translated into clinical practice will result in additional genomic and digital data to inform patient management. But for these data to have a positive clinical impact, physicians need the skills and tools to understand them and use them in a meaningful way. The pace of genomic discoveries and subsequent clinical implementation has been so rapid that even those beginning practice just 10 years ago missed out on contemporary genomics training in medical school. As a result, many physicians report being inadequately prepared to use genomic information for patient care.[37-39] This serves as a barrier to the implementation of genomic technologies into routine practice, and must be addressed to foster success for the PMI.[40,41] Consequently, as the PMI begins, initiatives are needed to create genomics resources and tools that are integrated into clinical practice to enable non-geneticist physicians to become proficient in practicing precision medicine.

In addition to the educational demand required for the PMI to impact clinical care, improved awareness of and support for the initiative itself among physicians is needed. A number of articles in prestigious medical journals have introduced the PMI,[4,41-44] but the necessary involvement of physicians in conducting baseline exams for patients enrolling, as well as the consequent role of the physician in answering patients' questions about the PMI and applying returned results to patient care, creates an imperative to generate support for the PMI among the physician and health

professional workforce. Studies have suggested that some physicians remain unsure that genomic information is clinically useful at this point in time,[37,45,46] creating a potential challenge in convincing physicians that the PMI is a worthwhile endeavor. In addition, the majority of physicians in practice have other competing demands on their time, including implementing new delivery models, participating in quality reporting initiatives, fulfilling meaningful use requirements, and utilizing new digital medicine technologies. Physicians will need to be convinced that the PMI should be prioritized among these competing demands.

*EHR and data challenges*

EHR capabilities. The health data collected as part of the PMI's national cohort has the potential to significantly impact clinical care—if it is accessible and meaningful to physicians. Robust and interoperable EHR systems and other health information technology (health IT) must be able to access and display longitudinal health data from each patient, no matter where that data is stored or whether it has been collected as part of the Cohort Program or by another health professional. Similarly, clinical decision support that will enable application of the data to care management is an essential component. However, many EHR systems in use today do not have such capabilities, and physicians are frustrated with the usability of EHR systems and report that they sometimes hamper safe and effective care.[47]

Significant improvements in EHR capabilities are needed for the essential data collection and sharing components of the PMI. The PMI Working group has cited some aspects of Meaningful Use (MU) Stage 3 that could contribute to the necessary innovation to facilitate the Cohort Program.[17] However, concern exists among physicians that the current MU program as well as Stage 3 create a significant barrier between the physician and patient by focusing on counting measure compliance and meeting arbitrary thresholds. Many, including the AMA, believe the Stage 3 MU proposal leaves many problems unanswered, diverts needed resources, and locks-in technology that will not assist patients and physicians in moving forward.[48] A number of private sector companies and organizations have made commitments to work with ONC on its S4S initiative, made up of pilot projects that aim to demonstrate new models that enable EHR data access, control, and management; and that would consequently improve care coordination among health professionals and researchers.[20,34] While S4S is an exciting opportunity for patients and PMI participants to manage their own complete medical record, MU requirements could stall the development of data standards and redirect EHR vendor priorities toward building systems based on a legacy framework.

Data accuracy and usability. While the PMI plans to return to each Cohort Program participant their own results and aggregated results from its studies, the participants' physicians may not automatically receive such results. Participants may have the opportunity to consent to sharing results directly with their physician. EHR capabilities may also dictate whether results will be deposited in the participant's EHR and are accessible to their physician. Physicians also will need to determine which of the returned results might impact patient care. Depending on the nature of the research being conducted, results may be applicable to patient care, for example, the results of a genetic test that identifies a clinically actionable variant; on the other hand, results may reveal the presence or absence of a biomarker that is still in experimental stages and not yet clinically informative. It is essential that physicians receive results that are applicable to patient care, and that mechanisms exist for physicians to receive other types of information should they desire and should the patient consent. Physician access to this data would ensure that it is appropriately explained to the patient in the context of his or her medical and family history, and that it is available to inform care when necessary.

Further, questions arise as to the quality and accuracy of the results, particularly those that are patient-generated. The PMI plans to collect behavioral and environmental data from participant self-reporting and from wearable sensors and applications.[17] These data could include diet, physical activity, tobacco and alcohol use, heart rate, respiratory rate, location, and environmental exposures.[17] While physicians may be interested in some of these measures, it will be difficult to verify the accuracy and quality of the data, and therefore to know whether it is trustworthy. An additional consideration is whether it belongs in the EHR and if so, how it would be deposited.

In addition, MU Stage 3 includes a requirement for physicians to accept patient-generated health data (PGHD), and certified EHRs must also support this function. PGHD are likely to play a role in precision medicine, yet methods for tagging and analyzing these data are still in development, and significant concerns exist about the privacy and security of this information. The mandate for PGHD also could mean that physicians will be required to purchase and implement poorly functioning EHRs and interpret voluminous, unstructured data that may not be accurate or clinically meaningful, detracting from the utility of health IT in the PMI.

## CONCLUSIONS

The PMI is an ambitious initiative that holds great promise for improving patient care and outcomes. It will require the coordination and commitment of both the federal and private sectors, and rests on the interest and willingness of participants to enroll and share their health data.

The scale of the PMI means that physicians are likely to have clinical encounters with participants enrolled in the Cohort Program. Ensuring that physicians are well-informed about the PMI and have the educational and health IT resources needed for such an endeavor is vitally important. The Council believes that the AMA is well-positioned to improve awareness of the PMI among physicians and to act as a resource for physicians who have questions about how it will impact their patients.

## RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of the report be filed.

1. That our American Medical Association work with the Precision Medicine Initiative to gather input from physicians to assist in the planning stages of the initiative and to improve awareness and willingness to recruit patients as participants. (Directive to Take Action)

2. That our AMA encourage the PMI to develop resources that will assist physicians in understanding the goals of the PMI, how to recruit and enroll patients, and how to best use the research results generated by it. (Directive to Take Action)

3. That our AMA continue to advocate for improvements to electronic health record systems that will enable interoperability and access while not creating additional burdens and usability challenges for physicians. (Directive to Take Action)

Fiscal Note: $50,000

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