JOINT REPORT OF THE COUNCIL ON MEDICAL SERVICE AND THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-17)
Payment and Coverage for Genetic/Genomic Precision Medicine
(Reference Committee J)

EXECUTIVE SUMMARY

The discovery of thousands of disease-related genes, aided by the mapping of the human genome, has led to medical innovations capable of dramatically improving patient-centered care and outcomes. Tens of thousands of genetic/genomic tests have been developed to screen for and diagnose diseases, tailor disease treatments, predict susceptibility to certain conditions, and inform prevention strategies. The number of targeted therapeutics capable of responding to particular genetic alterations has also increased exponentially, as have "companion diagnostics" tests that delineate which subpopulations will (or will not) benefit from particular therapeutics.

Precision medicine is a tailored approach to health care that accounts for individual variability in the genes, environment and lifestyle of each person. Physicians already practice precision medicine by managing each patient according to his or her unique symptoms, history, and preferences, but recent technological advances have vastly improved the ability to integrate genetic/genomic aspects of precision medicine into clinical practice. At the same time, new health care payment and delivery models are focused on value and require that health care services demonstrate their value to patients and the health care system as a prerequisite for payment and coverage.

Advanced bioinformatics programs are being used to generate scientific evidence of the validity of genetic/genomic tests and therapeutics and also increase understanding of many health conditions. Notably, there is considerable variability among public and private payers with regard to the evidentiary requirements for coverage of genetic/genomic precision medicine. Moreover, different insurers may review the same evidence yet reach conflicting conclusions about medical necessity and coverage of these services. The Councils initiated this joint report to provide an overview of genetic/genomic precision medicine and the current coverage and payment landscape; describe American Medical Association (AMA) policy and activity in this arena; and present policy recommendations that address inconsistencies in payment and coverage for genetic/genomic precision medicine services.

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CMS/CSAPH Joint Report I-17

Subject: Payment and Coverage for Genetic/Genomic Precision Medicine

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Referred to: Reference Committee J
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The discovery of thousands of disease-associated genes, aided by the mapping of the human genome in 2003, has led to medical innovations capable of dramatically improving patient-centered care and outcomes. As of July 2017, the National Institutes of Health's Genetic Testing Registry (GTR®), which is a central location for voluntary submission of genetic information by providers, included information on more than 52,000 genetic/genomic tests for more than 10,000 conditions.[1] These genetic/genomic tests help screen for and diagnose diseases, tailor disease treatments, predict susceptibility to certain conditions, and inform prevention strategies. The number of targeted therapeutics capable of responding to particular genetic alterations has also increased exponentially, as have "companion diagnostics" tests that delineate which subpopulations will (or will not) benefit from particular therapeutics.

Precision medicine is a tailored approach to health care that accounts for individual variability in the genes, environment and lifestyle of each person. Physicians already practice "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 (e.g., the human genome sequence), powerful methods for characterizing patients (e.g., 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. Precision medicine tests, technologies and therapeutics are increasingly being adopted into clinical practice as evidence of their effectiveness grows. At the same time, new health care payment and delivery models are focused on value and require that health care services demonstrate their value to patients and the health care system as a prerequisite for payment and coverage.

The Councils initiated this joint report to provide an overview of coverage and payment for genetic/genomic precision medicine; describe AMA policy and activity in this arena; and make policy recommendations. Genetic/genomic testing is used to analyze an individual's DNA and can confirm or rule out a suspected genetic condition or help determine an individual's chance of developing or passing on a genetic disorder. Environmental and behavioral data are also essential components of precision medicine, but unlike genetic/genomic data, their clinical use at this time is less common and coverage options are largely undeveloped. The term "genetic/genomic" is used throughout this report to refer to tests that analyze single genes or variants (genetic tests) as well as those that analyze larger portions of the genome, including multiple variants and/or genes, and whole exome and genome sequencing (genomic tests).

BACKGROUND

Precision medicine is routinely used in several specialties, most notably oncology. Using precision oncology, patients with certain cancers undergo testing that enables physicians to molecularly characterize their tumors, and tailor chemotherapy or other targeted therapeutics based on the genetic profile of their tumors. One common example is multi-variant panel tests that determine recurrence risk and potential response to chemotherapy in certain breast cancer patients. Outside of oncology, newborn screening, a state-based program in which every newborn is tested for dozens of genetic diseases that must be treated to avoid serious morbidity, is an example of precision medicine being applied on a large scale. Revolutionary advances in precision medicine have also enabled the diagnosis of rare and difficult-to-diagnose diseases, as well as the treatment of advanced-stage cancers and rare diseases that once were not treatable.

The potential exists for genetic/genomic precision medicine to be adopted more broadly into clinical practice because of advances in the technology used to collect and analyze huge sets of data, which has enabled enhanced research into genomic causes of disease and applications to clinical practice. The amount of data created with just one genome sequence is vast, and advanced bioinformatics programs are required to glean meaningful results from it. These data are being used to generate scientific evidence of the validity of genetic/genomic tests and therapeutics and also increase understanding of many health conditions. Despite these advances and initial evidence of improved health outcomes downstream, most patients do not have access to precision medicine because most public and private health insurers do not offer coverage for genetic/genomic services unless certain clinical criteria and evidentiary standards are met. As a result, access to this next generation of clinical testing services is often limited to individuals who can and choose to pay for it themselves, which has the potential to increase health disparities. While some consumers are paying for genetic tests on their own and without supervision of their physicians, many of these tests (often referred to as direct-to-consumer tests) have little clinical validity and may not be meaningful for physicians and patients. In April 2017, the Food and Drug Administration (FDA) approved marketing of certain direct-to-consumer genetic tests. Assuring the analytical and clinical validity of all clinical tests is critical to delivering optimal care to patients because not all tests are of the same quality and usefulness. Therefore, it is incumbent on physicians as well as payers to pay close attention to evaluations of the evidence supporting their clinical use.

PAYMENT AND COVERAGE

There is considerable variability among private and public payers with regard to the evidentiary requirements for coverage of genetic/genomic tests and services. Criteria used to evaluate tests and therapeutics generally include traditional measures such as analytical validity, clinical validity, and clinical utility. Analytical validity is the accuracy of the test in detecting the specific entity it was designed to detect without implying clinical significance such as diagnosis. Clinical validity is the accuracy with which a test identifies association of a specific entity (e.g., genetic variant) with a clinical purpose such as the presence, absence, predisposition to, or risk of a specific clinical condition. “Clinical utility” is a highly subjective term that does not have a universally accepted definition. Provider organizations, including national medical specialty societies, have defined this term to ensure that physicians are able to utilize testing when it is useful to physicians and patients by informing clinical care. Payers each define the term differently, with many adopting narrow definitions that require evidence of improved health outcomes downstream and that do not encompass the full value that a particular test or therapeutic may provide to patients, their families and society as a whole, such as establishing a diagnosis, reducing spending on continued diagnostic testing, and ending uncertainty for patients and their families. Clinical utility should refer to the

ability of a test to provide information related to the care of patients and to inform treatment decisions.

Currently, there is a well-established clinical evidence base to support coverage of a broad range of genetic/genomic tests; however, newer tests, which may be less expensive but for which the clinical evidence base has not yet matured, are rapidly and continuously becoming available. Because most insurers do not have the capability to assess the evidence for each test themselves they may require third-party health technology assessments (HTAs) which are then used in conjunction with other factors to make coverage determinations. HTA companies often look for evidence based on randomized controlled trials (RCTs)—which have historically been considered the gold standard for evidence generation—or comparable studies; however, the usefulness of many new genetic tests and therapeutics cannot feasibly be demonstrated using an RCT approach and may require novel research approaches. New genetic variants are being identified so rapidly that tests may need to be altered before RCTs can be completed. For example, variants that drive tumor growth and can potentially be targeted by a therapeutic are being identified and continually added to tumor testing panels. And for rare genetic diseases, RCTs may present ethical issues, take many years to complete, or never reach sufficient sample numbers.

HTAs may also require evidence not yet available that correlates genetic/genomic tests and therapies with clinical outcomes. A small study of private-payer challenges to establishing coverage of next-generation tumor sequencing (NGTS), which enables rapid examination of large numbers of genetic tumor alterations, found that most payers understand the potential benefits of NGTS.[2] However, a majority of payers interviewed for the study also reported that NGTS does not fit into their frameworks for medical necessity and does not meet their evidentiary standards requirements. For example, some NGTS tests identify variants for which a specific therapeutic does not yet exist or for which no clinical trials are underway. Despite the potential usefulness of knowing which variants are driving tumor growth for future clinical trials or new therapies, payers do not view such results as immediately actionable. Concerns among payers regarding implementation of NGTS and care delivery, such as the ability to effectively capture results in electronic health records and the preparedness of physicians to use the results in practice, are additional barriers to coverage.

Different types and levels of evidence are currently used to assess genetic/genomic tests, and some organizations—including the Agency for Healthcare Research and Quality, the American College of Medical Genetics and Genomics (ACMG), and the American Society of Clinical Oncology (ASCO)—evaluate available evidence and develop guidelines or recommendations for testing. AdvaMedDx—a trade association for diagnostics manufacturers—has developed a comprehensive framework for assessing the value of diagnostic tests and technologies based on four value drivers: clinical impact, non-clinical patient impact, care delivery revenue and cost impact, and population impact.

Medicare

Certain payers, including Palmetto GBA, a key Medicare contractor in the clinical testing domain, perform both a regulatory function—by requiring and assessing evidence of analytical/clinical validity—and a payer assessment of medical necessity. Medicare local coverage determinations (LCDs) regarding genetic/genomic tests have largely been developed by Palmetto GBA and then routinely adopted by other Medicare contractors in a process that has been lacking in transparency and sufficient stakeholder involvement to ensure that coverage decisions are in the best interests of patients. Several national medical specialty societies representing experts in molecular pathology have expressed serious concerns regarding the credibility of the evidence used by Palmetto GBA in

the drafting of LCDs that have denied coverage for certain genetic/genomic tests. Experts have stated that these LCDs lacked sufficient input, contradicted professional society practice guidelines, and encroached on physician clinical decision-making. As a result of the Palmetto GBA LCD process, the Centers for Medicare & Medicaid Services (CMS) does not cover many of the genetic/genomic tests that might be clinically meaningful to Medicare patients. According to the National Academies of Sciences, Engineering, and Medicine, as of April 2016, well over a thousand genetic tests had been excluded from Medicare coverage.[3]

Federal legislation (S. 794/H.R. 3635, "Local Coverage Determination Clarification Act") has been introduced to improve the LCD process and enable more patients to benefit from clinically validated medical innovations. This legislation would require Medicare contractors to establish a timely and open process for developing LCDs that includes open public meetings, meetings with stakeholders, an open comment period in the development of draft coverage policies, and a description of all evidence considered when drafting and finalizing coverage determinations. The LCD legislation would also require Medicare contractors seeking to adopt another contractor's proposal to independently evaluate the evidence needed to make a coverage determination, and would provide physicians and stakeholders a meaningful reconsideration process and options for appealing a Medicare contractor's decision to CMS. The AMA—along with the ACMG, ASCO, American Society for Radiation Oncology, American Society for Clinical Pathology, the Association for Molecular Pathology and the College of American Pathologists—supports the LCD legislation, which is consistent with AMA policy on LCDs.

Private Insurers

Private insurer coverage determination processes are neither transparent nor standardized across payers, and the evidence used by insurers to make coverage determinations regarding genetic/genomic tests and services can be inconsistent and convoluted. Just as coverage policies differ among insurers, their evidentiary standards requirements, interpretations of those standards, and evidence review processes vary as well. As a result, different insurers may review the same evidence of the validity and utility of a particular test or service yet reach conflicting conclusions about its medical necessity and coverage.

In addition to evidence-based evaluations of a genetic/genomic test's validity and utility, private payers often seek evidence of the service's cost-effectiveness, recommendations in professional society consensus statements or clinical practice guidelines, and peer-reviewed studies supporting its use.[4] One study examined private insurer coverage policies for cell-free DNA prenatal screening tests, which are routinely covered for high-risk pregnant women, to gain insights into payer decision-making for next-generation sequencing-based tests in general.[5] Most payers in this study used analytical and clinical validity and clinical utility to evaluate the evidence, and there was some variation in how they interpreted the evidence. This study also found that payers kept abreast of new peer-reviewed studies and professional society recommendations, and updated their coverage policies accordingly.[6]

Research into payer coverage of BRCA1/2 tests and gene panels has found that while nearly all payers covered BRCA1/2-only tests, gene panels that include BRCA1/2 were not likely to be covered because payers sought more evidence demonstrating the panels' clinical validity and clinical utility.[7] Gene panels identify more mutations than BRCA1/2-only tests but may also uncover incidental (or secondary) findings and variants of uncertain significance.[8] A study of payer-perceived challenges to covering hereditary cancer panels (HCPs) found that these panels may not be covered because they include variants or genes that have not been sufficiently studied and, as a consequence, the entire panel is considered investigational or experimental.[9] The study

highlights the complexity and uncertainty of the payment landscape by noting that while insurers generally do not cover HCPs, they may pay for them if, for example, they are billed for elements of the panel they considered medically necessary, or if payment denials are successfully appealed.[10] Payer policies may allow coverage of certain genetic/genomic tests and therapeutics under special circumstances or after successful appeal by physicians advocating on a patient's behalf. Physicians routinely advocate for patient access to testing that will inform diagnosis or management of disease, as well as patient access to therapeutics needed to treat disease; however, these efforts can be unduly burdensome.

On the front end, private insurers employ prior authorization, step therapy, and other forms of utilization management to control their members' access to certain services, including genetic/genomic testing and the treatments indicated by this testing. Utilization management requirements also involve very time-consuming processes that divert physician resources away from patient care. Prior authorization often interferes with patient care by either delaying that care or denying access to certain tests and therapeutics. Several large private insurers have established national prior authorization programs for genetic/genomic testing and will deny payment for services that have not been properly authorized or, in some cases, ordered by a geneticist or genetic counselor or carried out by insurer-approved laboratories. Some of these insurers have launched online, automated prior authorization programs for genetic/genomic testing. Certain insurers have instituted a stepwise approach to genetic/genomic testing, in which a less comprehensive test (assessing only one or a few variants or genes) must be ordered first and have inconclusive results before more comprehensive testing (sequencing of one or more entire genes or multiple variants) can be ordered. Insurers may also enforce limitations on the frequency of genetic testing, including sequencing, which is not appropriate in situations where test results may significantly change over time.

At least one large insurer requires physicians to use the insurer's own clinical decision support tool, which may not be compatible with physicians' EHRs and which may be viewed as potentially infringing on the clinical judgment of physicians. Certain national insurers have also instituted precertification requirements that require patients to receive pre-test genetic counseling from a board-certified genetic counselor or clinical geneticist before genetic tests can be ordered. These policies effectively reduce access to genetic testing for patients who do not have access to those professionals or are being treated by non-geneticist physicians who are fully capable of providing pre-test counseling. While AMA Policy H-480.944 supports genetic counseling, Policy H-460.902 opposes genetic testing restrictions based on specialty. A study of BRCA1/2 test cancellation rates during the periods before and after one national insurer began mandating pre-test counseling by genetic counselors or clinical geneticists found that the mandate significantly reduced patient access to testing.[11]

Cost-effectiveness

Health care costs continue to rise despite widespread efforts to insert value into models of care delivery and benefit design. Accordingly, cost-effectiveness, affordability, and value are critical to the Councils' discussion of precision medicine and the growing market of genetic/genomic tests and therapeutics. Although whole genome sequencing has become much more affordable than it once was, most multi-variant tests are expensive, ranging from $500 to $5000. Single gene tests may cost as low as about $100 for targeted mutation analysis (testing for one or a few variants in the gene) and approximately $500 for sequencing the entire gene.

For many genetic/genomic tests, there is widespread variability in the test's price as well as payment and coverage for that test, which must be sorted out by ordering physicians who must also

take into account patient cost-sharing expenses. In some cases, patients may request genetic/genomic testing that is not covered by insurance and is instead purchased directly from a test company at an entirely different price. Cost comparison tools (e.g., Fair Health) can be used by patients and physicians to estimate the costs of some genetic tests and services.

More research is needed to demonstrate the cost-effectiveness and economic value of precision medicine. A 2014 study concluded that many genetic tests are cost-effective but fewer are cost saving. Notably, a large number of available tests have not yet been evaluated.[12] A systematic review of economic evaluations of genetic and pharmacogenetics tests found that only 21 percent of pharmacogenetics tests and 12 percent of predictive genetic tests are cost saving. Reporting of incidental/secondary findings using sequencing technologies has been found to be cost-effective in certain circumstances but not necessarily cost saving in healthy populations unless the cost of the sequencing is below a certain threshold.[13,14]

Genetic Discrimination and Privacy

In 2008, after 13 years of effort on the part of many advocacy organizations including the AMA, Congress passed the Genetic Information Nondiscrimination Act (GINA) nearly unanimously. Title I of GINA prohibits group and individual health insurers from using a person's genetic information in determining eligibility or premiums and prohibits health insurers from requesting or requiring that a person undergo a genetic test in order to collect genetic information on that person for underwriting decisions. Importantly, GINA does not prohibit health insurance underwriting based on current health status, including manifest disease of a genetic nature. Rather, it is intended to protect individuals with a genetic predisposition to disease that has not manifested, whether or not an individual has knowledge about that predisposition based on his or her own genetic test results or the genetic test results or manifestation of disease in a family member. Since the enactment of GINA, only a modest number of genetic discrimination complaints have been filed under its provisions; in 2016, 238 cases of genetic discrimination were filed out of nearly 100,000 total discrimination cases filed.[15] It is possible that the small number of cases reflects the effectiveness of GINA at discouraging the practice of discrimination on the basis of genetics by health insurers, or alternatively, that discrimination is occurring but is unrecognized or unreported.

Fears about genetic discrimination have led to refusal by some to undergo genetic testing.[16,17,18] This can have serious health implications for individuals for whom genetic testing would be beneficial. Even among those who do undergo genetic testing, many withhold test results from their physicians, and some request that their results be placed in a "shadow chart" or withheld entirely from their medical record. Information that is not available to physicians can have detrimental effects on patient care because treating physicians unfamiliar with the patient will have no knowledge of genetic test results unless that information is volunteered by the patient. With more frequent use of technologies that involve analysis of patients' genomic information, the potential for misuse and discrimination grows. A very important additional consideration is how difficult it has become to maintain the privacy and security of genomic information. In October 2012, the Presidential Commission for the Study of Bioethical Issues concluded that efforts to de-identify genetic information are exceptionally challenging and will gradually become impossible.[19] In January 2013, a group of scientists demonstrated that the genetic information provided by individuals who had been assured anonymity could in fact be re-identified.[20,21,22] Therefore, given the rapid uptake of genomic-based technologies in both the clinical setting and outside the clinic, there is a pressing need to remain vigilant on policies that protect the privacy of individuals' genetic information.

Physician Education

Educating physicians about precision medicine, including genetic/genomic testing and therapeutics, presents its own unique challenges, given the rapid pace of discoveries as well as extensively documented physician time constraints. Physicians must have the knowledge and skills to integrate precision medicine into their clinical practice for obvious reasons related to professionalism and patient care, and also to effectively advocate for insurer coverage of valid and meaningful genetic/genomic tests and targeted therapeutics. From a payment perspective, physicians will likely need more time for counseling patients and to analyze and explain genetic test results, and they should be adequately paid for these services. Patients who have paid for direct-to-consumer testing may also present genetic risk factor findings to their physicians, who are then challenged to consider how to explain the test results and also justify payment for clinical follow-up. Additionally, laboratories providing the tests are increasingly requesting large quantities of documentation from physicians that are needed for retrospective reviews.

The technical complexity of precision medicine adds to the hurdles faced by physicians interested in integrating this type of care into their practices. Training and implementation costs associated with adopting new care practices must be taken into consideration. As in many areas of medicine, there is also the need for significant health information technology (health IT) improvements that will enable interoperability, access, and clinical decision support while not creating additional burdens and usability challenges for physicians.

AMA ACTIVITY

In recent years, the AMA House of Delegates has established relevant policies recommended by the councils. The Council on Science and Public Health (CSAPH) has addressed several topics related to precision medicine including genome editing (CSAPH Report 3-I-16), genomics in hypertension (CSAPH Report 1-I-14), genomics in type 2 diabetes (CSAPH Report 2-A-14), genetic discrimination (CSAPH Report 7-A-13), and next-generation genomic sequencing (CSAPH Report 4-I-12). CSAPH Report 3-A-16 discusses the Precision Medicine Initiative (PMI), now called the All of Us initiative, which is creating a research cohort of over one million volunteers who will share their genetic, environmental and lifestyle data.

The Council on Medical Service developed Report 2-A-13 on value-based insurance design; Report 7-A-14 on coverage and payment for telemedicine; Report 5-I-16 on incorporating value into pharmaceutical pricing; and Report 6-I-16 on integrating mobile health applications and devices into clinical practice.

Regulatory Activity

Uncertainties in the oversight and regulation of genetic/genomic testing services have the potential to stifle innovation and impede patient access to what could be transformative, life-altering care. The AMA, in collaboration with several national medical specialty societies, has developed legislative principles (https://www.ama-assn.org/sites/default/files/media-browser/public/genetics/personalized-medicine-guiding-principles.pdf) to guide its advocacy efforts in this arena. The principles make clear that payment and coverage policies should not dictate which diagnostic or treatment options are available to physicians and patients, and should take into account the role of physicians in driving and applying genetic/genomic innovations. Furthermore, the principles reinforce that testing alone will not dictate treatment. Rather, physicians' diagnostic impressions and their interpretation of test results in the context of the patient's clinical situation and preferences should guide treatment options. Since regulation of

genetic tests is integral to physician practice and patient care, the AMA is engaged in ongoing advocacy with policymakers and other stakeholders to preserve the physician's role in all aspects of patient care, including the oversight of laboratory-developed tests and other components of precision medicine.

The AMA actively 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. Accordingly, the AMA has made public comments and statements opposing FDA oversight activities that infringe on the practice of medicine, and is engaged with a broad group of stakeholders to support regulatory reform for genetic tests that promotes innovation and preserves patient access. The AMA has also urged Congress to pursue modernization of the CLIA oversight framework for high complexity laboratory testing services that would establish standards for clinical validity and strengthen established standards related to quality control and quality assurance, and to personnel standards including regular proficiency testing. Strengthening the existing CLIA oversight framework will assure patient safety and provide a stronger structure to prevent laboratory errors while preserving patient access to care.

Protecting Access to Medicare Act (PAMA)

Section 216 of the Protecting Access to Medicare Act (PAMA), which was enacted in 2014, significantly revised the Medicare payment system for clinical tests by requiring that Medicare payment for laboratories be based on the weighted median of private payer rates. Regulations issued by CMS in June 2016 required laboratories that provide clinical testing, including certain physician office-based laboratories, to collect and report private payer payment and test volume data to CMS. CMS is using this private payer data to set new payment rates that will become effective on January 1, 2018.

The AMA has urged CMS to implement a number of measures to ensure the accuracy of the new payment rates, which will be based on a retrospective reporting period for data collection from 2016. The AMA has expressed serious concerns to CMS regarding the integrity of the data that will be used to calculate the new payment rates, and whether the rates will accurately reflect the weighted median of private payer payments, as Congress intended. Based on the lack of data integrity, the AMA and other stakeholders anticipate that the new payment rates could effectively reduce patient access to clinical lab testing. The AMA also continues to urge CMS to ensure that implementation of the new payment rates results in as little administrative burden for physicians as possible.

PAMA regulations also required CMS to issue Healthcare Common Procedure Coding System (HCPCS) codes to identify new advanced diagnostic laboratory tests (ADLTs), and clinical tests that are cleared or approved by the FDA (referred to as Clinical Diagnostic Laboratory Tests, or CDLTs), if an applicable Current Procedural Terminology (CPT) code (HCPCS level I) does not exist; and to provide, upon request, either a HCPCS code or unique identifier for test tracking and monitoring. In order to address these coding provisions, the CPT Editorial Panel approved in November 2015, and finalized at its February 2016 panel meeting, the new Proprietary Laboratory Analyses (PLA) section of the CPT code set. PLA codes include a descriptor for laboratories or manufacturers that want to more specifically identify their tests. An important part of the development of this new set of codes is that industry and other stakeholders, including subject matter experts, actively participate in the PLA process. To that end, the Panel created the Proprietary Laboratory Analyses Technical Advisory Group (PLA-TAG) to advise the Panel on applications received for codes to be added to the PLA section of CPT. Along with representation

by the Panel and certain Panel workgroups, the PLA-TAG is composed of individuals with expertise relating to the services covered under the CPT PLA section. These include, but are not limited to, members from various industry segments such as independent laboratories, private payers, professional/industry organizations, commercial laboratories, academic medical institutions and private practitioners. Members of the PLA-TAG will play a crucial role in the PLA code creation process by reviewing CPT PLA code change applications and making recommendations regarding these requests for CPT codes that describe ADLTs or CDLTs.

Prior Authorization

Due to its widespread usage and the significant administrative and clinical concerns it can present, the AMA addresses prior authorization through a multifaceted approach that includes a number of high-profile activities, including the release of Prior Authorization and Utilization Management Reform Principles to address priority concerns. The principles were developed by a workgroup of state and national medical specialty societies, national provider associations and patient representatives convened by the AMA. The 21 principles (https://www.ama-assn.org/sites/default/files/media-browser/principles-with-signatory-page-for-slsc.pdf) seek to improve prior authorization and utilization management programs by addressing broad categories of concern including: clinical validity; continuity of care; transparency and fairness; timely access and administrative efficiency; and alternatives and exemptions. Health plans, benefit managers and any other parties conducting utilization management, as well as accreditation organizations, have been urged to apply the principles to both medical and pharmacy benefits. The principles, which have gained widespread support since their release, with over 100 stakeholder organizations signing on in support of their objectives, include the following:

- Any utilization management program applied to a service, device or drug should be based on accurate and up-to-date clinical criteria and never cost alone. The referenced clinical information should be readily available to the prescribing/ordering provider and the public.
- Utilization management programs should allow for flexibility, including the timely overriding of step therapy requirements and appeal of prior authorization denials.
- Utilization review entities should offer an appeals system for their utilization management programs that allows a prescribing/ordering provider direct access to a provider of the same training and specialty/subspecialty for discussion of medical necessity.

The AMA has also engaged in two research projects to gather data on the impact of prior authorization on patients and physician practices. A web-based survey of 1000 practicing physicians conducted with a market research partner in December 2016 found that practices complete an average of 37 prior authorizations per physician per week, which take the physician and his/her staff an average of 16 hours—the equivalent of two business days—to process. Ninety percent of physicians reported that prior authorization delays patients' access to necessary care. The survey results (https://www.ama-assn.org/sites/default/files/media-browser/public/government/advocacy/2016-pa-survey-results.pdf) serve as a valuable framework for the aforementioned principles and have provided a strong evidence base for AMA advocacy efforts related to prior authorization. The AMA is also partnering on an academic research project seeking to measure the overall impact of prior authorization on health care costs and outcomes.

The AMA also works closely with state medical associations and national medical specialty societies to address prior authorization and other utilization management issues through state legislation. Several bills passed by state legislatures have been based on the AMA's model legislation, the "Ensuring Transparency in Prior Authorization Act" (https://www.ama-assn.org/sites/default/files/media-browser/specialty%20group/arc/model-bill-ensuring-

transparency-in-prior-authorization.pdf). The AMA's Prior Authorization Toolkit (https://www.ama-assn.org/system/files/media-browser/premium/psa/prior-authorization-toolkit_0.pdf) provides a useful overview of the current prior authorization landscape and tips for reducing practice burdens related to prior authorization, including implementation of standard electronic processes. In sum, prior authorization and other utilization management programs are high-priority targets for the AMA.

Educating Physicians

The AMA recognizes the importance of educating physicians and physicians-in-training about the clinical uses and ethical considerations of genetic/genomic services. To assist physicians who are encountering new precision medicine technologies, the AMA has partnered with Scripps Translational Science Institute and The Jackson Laboratory to develop "Precision Medicine for Your Practice" (http://education.ama-assn.org/precision-medicine.html), a series of short, online continuing medical educational modules covering specific topics in genomics and precision medicine, including expanded carrier screening in prenatal care, prenatal cell-free DNA screening, somatic cancer panel testing, large scale sequencing in the healthy individual, large scale sequencing as a diagnostic tool, and pharmacogenomics. In the near future, the AMA will be adding modules on sequencing the healthy individual, pharmacogenomics and neurogenomics.

Additionally, the AMA is carrying out research to identify physicians' educational and resource needs for appropriate implementation of precision medicine into practice. The AMA will continue to develop tools to assist physicians with precision medicine needs.

AMA and All of Us Initiative

As part of its pledge to assist with the PMI, which includes the All of Us Research Program, the AMA is committed to actively working to improve patient access to personal medical information and helping physicians leverage electronic tools to make health information more readily available; developing and disseminating resources including toolkits, podcasts and fact sheets; and improving awareness of the PMI/All of Us Initiative, and how to enroll in its cohort, among physicians.

Health IT and Digital Health

Significant improvements in EHR and other health IT capabilities are critically needed for precision medicine to reach its potential. Robust and interoperable health IT systems must be able to access and display longitudinal health data from each patient regardless of where the data is stored. EHRs are rich with biological, behavioral and environmental data; however, impediments to accessing and enabling the secure exchange of data across health care systems must be overcome. Clinical decision support that will enable application of the data to care management is also 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. The AMA actively promotes EHRs that can provide clinical decision support and use genetic/genomic data to provide clinically meaningful information to physicians.

Beyond EHRs, the AMA is committed to understanding and influencing the evolution of health IT and digital health, both of which are integral to the implementation of precision medicine. The AMA provides leadership on digital solutions involving telemedicine and telehealth, mobile health, wearables, and remote monitoring. Using the expertise of physicians and input from partners on the leading edge of health technology, the AMA has developed resources, toolkits and training to help physicians navigate and maximize technology for improved patient care.

AMA POLICY

Policy H-460.908 acknowledges the increasingly important role of genomic-based personalized medicine applications in the delivery of care; calls for the development of educational resources and tools to assist in the clinical implementation of genomic-based personalized medicine; and directs the AMA to continue to represent physicians' voices and interests in national policy discussions of issues pertaining to the clinical implementation of genomic-based personalized medicine, such as genetic test regulation, clinical validity and utility evidence development, insurance coverage of genetic services, direct-to-consumer genetic testing, and privacy of genetic information. Policy D-460.968 supports the AMA's work with the PMI and also advocates for improvements to electronic health record systems that will enable interoperability and access without creating additional burdens and usability challenges for physicians.

Policy D-460.976 directs the AMA to maintain a visible presence in genetics and molecular medicine. Policy H-480.944 supports appropriate use of genetic testing, pre- and post-test counseling for patients undergoing testing, and physician preparedness in counseling patients or referring them to qualified genetics specialists, as well as the development of best practice standards concerning pre- and post-test genetic counseling. Under Policy H-460.902, the AMA opposes limiting the ordering of genetic testing based solely on physician specialty. The clinical application of next generation genomic sequencing is addressed by Policy H-460.905, while genome analysis and variant identification is the subject of Policy D-460.971. Policy D-480.987 focuses on direct-to-consumer marketing and availability of genetic tests, and recommends that genetic testing be carried out under the supervision of a qualified health professional. Policy H-65.969 strongly opposes discrimination based on genetic information.

Policy H-185.939 supports flexibility in the design and implementation of value-based insurance design (VBID), which explicitly considers the clinical value of a given service or treatment when determining cost-sharing structures or other benefit design elements. Policy H-185.939 calls for active involvement of practicing physicians; the use of high-quality, evidence-based data; and transparency of the methodology and criteria used to determine high- or low-value services or treatments and coverage and cost-sharing policies. The policy states that VBID should not restrict access to patient care and must include an appeals process to enable patients to secure care recommended by their physicians. The policy also calls for plan sponsors to engage in ongoing evaluation of the plan designs to ensure VBID coverage rules are updated in accordance with evolving clinical evidence.

AMA policy promotes price transparency and education regarding cost-sharing by health plans (Policies D-155.987 and H-165.828). Policy H-320.949 states that utilization management criteria should be based on sound clinical evidence, permit variation to account for individual patient differences, and allow physicians to appeal decisions. Policy D-330.908 advocates for improvements in the LCD process, including increased transparency and a prohibition on Medicare contractors adopting another contractor's LCD without a full and independent review. Policy D-330.918 directs the AMA to work with national medical specialty societies and CMS to identify outdated coverage decisions that create obstacles to clinically appropriate patient care. Policy H-460.909 outlines principles for comparative effectiveness research, and Policy D-390.961 advocates for adequate investment in this type of research and also better methods of data collection, development, reporting and dissemination of practical clinical decision-making tools. Policy H-155.960 promotes value-based decision-making, collection of clinical and cost data, and cost-effectiveness research, while principles to guide value-based decision-making are delineated in Policy H-450.938.

DISCUSSION

The Councils' work on precision medicine is timely given passage of the *21st Century Cures Act* and continued funding of the PMI, including the All of Us Research Program, and the Cancer Moonshot. The speed and volume of advances in genetics and genomics are impacting an array of regulatory, coding and payment processes that remain very fluid and will continue to be closely monitored by the AMA so that the physician perspective is clearly articulated. As with past health care innovations, the initial period of implementation of genetic/genomic precision medicine is complex and costly. Payers, policymakers and other stakeholders are challenged to keep up with the rapid development of new tests and technologies and the generation of evidence supporting their use, which are essential to ensuring patient safety while also preventing delays in payment and coverage for valid and meaningful services. In the long run, the Councils anticipate that genetic/genomic precision medicine services will become more affordable and in the mainstream across a variety of medical specialties.

The Councils' recommendations build upon existing AMA policy to establish new, foundational policy addressing the inconsistencies in payment and coverage of genetic/genomic precision medicine services. The Councils recommend reaffirmation of seven integral policies: Policy H-460.968, which directs the AMA's work on the PMI; Policy H-460.908, which directs the AMA to continue engaging in policy discussions related to the clinical implementation of genetics/genomics; Policy D-480.987, which focuses on direct-to-consumer marketing and availability of genetic testing; Policy H-185.939, which supports implementation of value-based insurance design, consistent with a series of principles regarding the clinical value of treatments and services; Policy H-329.949, which focuses on utilization management-related barriers to care; Policy H-65.969, which opposes discrimination based on genetic information; and Policy H-460.902, which opposes limitations by payers on the ordering of genetic testing based solely on physician specialty.

The Councils discussed the importance of sharing genomic variant data and ensuring that patients and physicians are notified of clinical significance changes. The Councils recommend adding a third clause to Policy D-460.971, which would encourage laboratories to establish a process by which patients and their physicians could be notified when interpretation and clinical significance changes for previously reported variants.

The Councils are concerned by the lack of transparency and standardization across payer coverage determination processes, which may hinder access to valid and meaningful tests and therapeutics as well as future innovations. Accordingly, the Councils recommend that the AMA encourage public and private payers to adopt processes and methodologies for determining coverage and payment for genetic/genomic precision medicine that promote transparency and clarity; involve stakeholders across disciplines, including genetic/genomic medicine experts; describe the evidence being considered and methods for updating the evidence; provide opportunities for comment and meaningful reconsiderations; and incorporate value assessments that consider the value of genetic/genomic tests and therapeutics to patients, families and society as a whole.

The Councils further recognize that the usefulness of many new genetic tests and therapeutics cannot feasibly be demonstrated using an RCT approach and will require novel research approaches. Accordingly, the Councils recommend that the AMA encourage coverage and payment policies for genetic/genomic precision medicine that are evidence-based and take into account the unique challenges of traditional evidence development through RCTs, and work with test developers to establish clear thresholds for acceptable evidence for coverage.

Because patient access to genetic/genomic precision medicine services is largely dependent on public and private insurer decisions to pay for them, the Councils recommend that the AMA work with national medical specialty societies and other stakeholders to encourage the development of a comprehensive payment strategy that facilitates more consistent coverage of genetic/genomic tests and therapeutics.

As additional steps toward timely and appropriate application of precision medicine into practice, the Councils recommend that the AMA encourage national medical specialty societies to develop clinical practice guidelines incorporating precision medicine approaches that support adoption of appropriate, evidence-based services; and support continued research and evidence generation demonstrating the validity, meaningfulness, cost-effectiveness and value of precision medicine.

Finally, the Councils recognize that the payment and coverage landscape for precision medicine is evolving, and emphasize that the Councils' work is ongoing. Future studies may be warranted by further innovation and as new technologies—such as artificial intelligence—are adopted into clinical practice.

RECOMMENDATIONS

The Council on Medical Service and the Council on Science and Public Health recommend that the following be adopted and that the remainder of the report be filed:

1. That our American Medical Association (AMA) reaffirm Policy H-460.908, which directs our AMA to continue representing physicians in policy discussions of issues related to the clinical implementation of genomic-based medicine, such as genetic test regulation, clinical validity and utility evidence development, insurance coverage of genetic services, direct-to-consumer genetic testing, and privacy of genetic information. (Reaffirm HOD Policy)

2. That our AMA reaffirm Policy D-480.987, which recommends that genetic testing be carried out under the supervision of a qualified health professional; encourages individuals interested in obtaining genetic testing to contact a qualified health professional; and directs the AMA to educate and inform physicians on the types of genetic tests available directly to consumers. (Reaffirm HOD Policy)

3. That our AMA reaffirm Policy H-185.939, which supports flexibility in the design and implementation of value-based insurance design programs consistent with a series of principles regarding the clinical value of treatments and services. (Reaffirm HOD Policy)

4. That our AMA reaffirm Policy H-65.969, which strongly opposes discrimination based on an individual's genetic information; support legislation that protects against genetic discrimination and misuse of genetic information; and supports education for health care providers and patients on the protections against genetic discrimination currently afforded by federal and state laws. (Reaffirm HOD Policy)

5. That our AMA reaffirm Policy H-460.902, which opposes limitations by public and private payers on the ordering of genetic testing that are based solely on physician specialty. (Reaffirm HOD Policy)

6. That our AMA encourage public and private payers to adopt processes and methodologies for determining coverage and payment for genetic/genomic precision medicine that:

a. Promote transparency and clarity;
b. Involve multidisciplinary stakeholders, including genetic/genomic medicine experts and relevant national medical specialty societies;
c. Describe the evidence being considered and methods for updating the evidence;
d. Provide opportunities for comment and review as well as meaningful reconsiderations; and
e. Incorporate value assessments that consider the value of genetic/genomic tests and therapeutics to patients, families and society as a whole, including the impact on quality of life and survival. (New HOD Policy)

7. That our AMA encourage coverage and payment policies for genetic/genomic precision medicine that are evidence-based and take into account the unique challenges of traditional evidence development through randomized controlled trials, and work with test developers and appropriate clinical experts to establish clear thresholds for acceptable evidence for coverage. (New HOD Policy)

8. That our AMA work with interested national medical specialty societies and other stakeholders to encourage the development of a comprehensive payment strategy that facilitates more consistent coverage of genetic/genomic tests and therapeutics that have clinical impact. (New HOD Policy)

9. That our AMA encourage national medical specialty societies to develop clinical practice guidelines incorporating precision medicine approaches that support adoption of appropriate, evidence-based services. (New HOD Policy)

10. That our AMA support continued research and evidence generation demonstrating the validity, meaningfulness, short-term and long-term cost-effectiveness and value of precision medicine. (New HOD Policy)

Fiscal Note: Less than $500

REFERENCES

[1] National Institutes of Health. Genetic Testing Registry. Accessed online at https://www.ncbi.nlm.nih.gov/gtr/ on July 14, 2017.
[2] Trosman JR, Weldon CB, Kelley K et al. Challenges of coverage policy development for next-generation tumor sequencing panels: Experts and payers weigh in. *Journal of the National Comprehensive Cancer Network*. 2015: 13(3): 311-318.
[3] National Academies of Sciences, Engineering, and Medicine. An evidence framework for genetic testing. Washington, DC: The National Academies Press. 2017. Doi: 10.17226/24632.
[4] *Id.*
[5] Dervan AP, Deverka PA, Trosman JR et al. Payer decision-making for next-generation sequencing-based genetic tests: insights from cell-free DNA prenatal screening. *Genetics in Medicine*. 2017. May;19(5):559-567. doi: 10.1038/gim.2016.145.
[6] *Id*.
[7] Clain E, Trosman JR, Douglas MP et al. Availability and payer coverage of BRCA1/2 tests and gene panels. Nat Biotechnol. 2015 September 8;33(9):900-912. Doi:10.1038/nbt.3322.
[8] *Id*.
[9] Trosman JR, Weldon CB, Douglas, MP et al. Payer coverage for hereditary cancer panels: barriers, opportunities, and implications for the Precision Medicine Initiative. *J Natl Compr Canc Netw*. 2017 February; 15(2):219-228.
[10] *Id*.
[11] Whitworth P, Beitsch P, Arnell C et al. Impact of payer constraints on access to genetic testing. *Journal of Oncology Practice*. 2016. Doi: 10.1200/JOP.2016.013581.
[12] Phillips KA, Sakowski JA, Trosman J et al. The economic value of personalized medicine tests: what we know and what we need to know. *Genetics in Medicine*. 2014 March; 16(3);251-257. Doi:10.1038/gim.2013.122.
[13] Bennette CS, Gallego CJ, Burke, W et al. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. *Genetics in Medicine*. 2015; 17:587-595. Doi:10.1038/gim.2014.156
[14] Phillips KA, Ladabaum U, Pletcher MJ et al. Key emerging themes for assessing the cost-effectiveness of reporting incidental findings. *Genetics in Medicine*. 2015 April; 17(4): 314-315. Doi: 10.1038/gim.2015.13.
[15] Equal Employment Opportunities Commission. Genetic Information Nondiscrimination Act Charges.
[16] Lapham EV, Kozma C, Weiss JO. Genetic discrimination: perspectives of consumers. *Science*. 1996;274(5287):621-624.
[17] Hadley DW, Jenkins J, Dimond E, et al. Genetic counseling and testing in families with hereditary nonpolyposis colorectal cancer. Archives of Internal Medicine. 2003;163(5):573-582.
[18] Peterson EA, Milliron KJ, Lewis KE, Goold SD, Merajver SD. Health insurance and discrimination concerns and BRCA1/2 testing in a clinical population. Cancer Epidemiol Biomarkers Prev. 2002;11(1):79-87.
[19] Presidential Commission for the Study of Bioethical Issues. Privacy and Progress in Whole Genome Sequencing. 2012.
[20] Gymrek M, McGuire AL, Golan D et al. Identifying personal genomes by surname interference. *Science*. 2013;339(6117):321-4.
[21] Rodriguez LL, Brooks LD, Greenberg JH et al. Research ethics. The complexities of genomic identifiability. *Science*. 2013;339(6117):275-6.
[22] Bohannon J. Geneology databases enable naming of anonymous DNA donors. *Science*. 2013;339(7117):262.