REPORTS OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

The following reports, 1–5, were presented by Sandra A. Fryhofer, MD, Chair:

1. USE OF ATYPICAL ANTIPSYCHOTICS IN PEDIATRIC PATIENTS

Reference committee hearing: see report of Reference Committee K.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AND REMAINDER OF REPORT FILED
See Policy D-120.950.

INTRODUCTION

Policy D-120.955 – The Use of Atypical Antipsychotic Medication in Pediatric Patients, directed the Council on Science and Public Health to prepare a report on the safety and appropriate use of atypical antipsychotic medications in children and adolescents. In 2011, the American Academy of Child and Adolescent Psychiatry (AACAP) published a practice parameter on the use of atypical antipsychotics in pediatric patients.[1] Guidance on the clinical use of these drugs in pediatric patients also has been developed by the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guideline Project Group.[2,3] This report addresses safety and appropriate use and briefly discusses the complex issues surrounding the clinical use of these drugs in pediatric patients, evaluating new data, and referencing clinical recommendations that are intended to improve outcomes when atypical antipsychotics are used in pediatric patients.

METHODS

Information for this report was obtained from English-language reports selected from a PubMed search for article titles for the terms “olanzapine,” “ziprasidone,” “clozapine,” “aripiprazole,” “risperidone,” “paliperidone,” “ asenapine,” “iloperidone,” “lurasidone,” or “quetiapine” combined with the terms “child*,” “adolescent*” or “pediatric*,” in the title or abstract and applying filters corresponding to systematic reviews, randomized controlled trials, clinical trials or case reports. Additionally, the Cochrane Library clinical trial database and the federal registry of clinical trials (www.clinicaltrials.gov) were searched using the same strategy. Further information was obtained from the Internet site of AACAP. Pharmaceutical companies that were original patent holders for atypical antipsychotics were invited to supply bibliographies as well.

ATYPICAL ANTIPSYCHOTIC DRUGS

Definition

Compared with conventional antipsychotic drugs such as haloperidol, atypical antipsychotics have a substantially lower propensity for inducing extrapyramidal nervous system symptoms (EPS) (i.e., parkinsonism, dystonia, akathisia, and tardive dyskinesia). This feature represents the most significant clinical advantage of atypical antipsychotics. Serum prolactin concentrations also are less affected compared with older antipsychotic drugs, except for risperidone.

Currently Marketed Atypical Agents

Atypical agents include clozapine, paliperidone (metabolite of risperidone), olanzapine, quetiapine, ziprasidone, aripiprazole, risperidone, asenapine, iloperidone, and lurasidone (see Table). With the exception of aripiprazole, which is a partial agonist, atypical antipsychotic drugs (like their conventional counterparts) antagonize dopamine 2 receptors but also exhibit variable affinity for blocking other dopamine receptor subtypes. Atypical antipsychotics also generally antagonize serotonin 2A and 2C receptors with variable antagonist activity at histamine, muscarinic, and alpha-adrenergic receptors; some also function as agonists or partial agonists at serotonin 1A receptors. For a summary chart detailing these variable receptor activities see McDonagh et al.[4] As a group, these drugs have diverse pharmacodynamic properties and exhibit variable clinical responses, especially with respect to adverse effects. Little

or no information is available on the use of asenapine and iloperidone in pediatric patients and these agents are not further discussed.

Clinical Efficacy and Safety

Atypical agents are similar to conventional drugs in reducing psychotic symptoms (and may be more effective in reducing so-called negative symptoms). Although they produce fewer neurologic side effects, evidence of superior efficacy in adult patients with schizophrenia has been neither consistent nor robust, except for clozapine, which can cause severe hematologic side effects that limit its pattern of use. More recently, even the putative safety advantages of atypical antipsychotics have been questioned because they present their own spectrum of adverse effects including hypotension, seizures, weight gain, increased risk of type II diabetes and hyperlipidemia; some of these drugs may lengthen the QT interval as well.

Clinical Uses of Atypical Antipsychotic Drugs in Pediatric Patients

Labeled Indications. Risperidone, olanzapine, aripiprazole, quetiapine, and paliperidone have FDA-approved uses in pediatric patients. All five are approved for the treatment of schizophrenia in adolescents 13 to 17 years of age. Olanzapine is approved for the acute treatment of manic or mixed episodes and maintenance treatment of bipolar I disorder in adolescents. This approval is extended down to the age of 10 years for aripiprazole and risperidone, although risperidone is approved only for short term use. Aripiprazole and risperidone also are approved for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age.

Off-Label Uses. Atypical antipsychotics are used off-label to treat Tourette syndrome and tic disorders, attention deficit hyperactivity disorder (ADHD), and pervasive developmental disorder. They also have been increasingly used to treat oppositional behavior, irritability and aggressive behaviors across various diagnostic categories. Case reports and open label trials also indicate they are being used in pediatric patients with borderline personality disorder, obsessive compulsive and other anxiety disorders, anorexia nervosa, mental retardation/developmental delay, Axis I disorders that include psychotic features, as adjunctive therapy in major depressive disorder, and in patients with delirium (references supplied on request).

Trends in Prescribing of Antipsychotics

Based on data obtained from IMS Health, total antipsychotic use (conventional plus atypical) increased from more than 6 million treatment visits[*] in 1995 to 16.7 million visits in 2006, declining to 14.3 million visits in 2008.[5] By 2011, U.S. spending on prescriptions for all antipsychotic medications was estimated at $18.2 billion, trailing only medications used for diabetes, hyperlipidemia, respiratory disease, and cancer.[6] The proportional use of atypical antipsychotics was 16% of treatment visits in 1995, but such use had surged to 93% of treatment visits by 2008. In two-thirds of these visits, the prescription was for an off-label use.[5]

Antipsychotic treatment rates among privately insured youth ages 6 to 17 increased steadily from 1996 (0.21%) to 2006 (0.90%) with higher rates among those ages 13 to 17.[7] The annualized rate of use in such patients ages 2 to 5 more than doubled between 1999 and 2007 to 0.16%, most commonly to help manage pervasive developmental disorder or mental retardation.[8]

More than 4% of Medicaid youth ages 6 to 17 filled at least one prescription for an antipsychotic in 2004, with 75% of these being for off-label uses.[7] A number of children under 6 years of age enrolled in Medicaid programs receive ongoing treatment with antipsychotic medications.[9,10]

Safety

While all atypical antipsychotics are associated with metabolic changes that may increase cardiovascular risk, each drug has its own risk profile. The chief concerns are weight gain, hyperlipidemia, glucose intolerance, and extrapyramidal side effects. Based on analysis of short term trials (3 to 12 weeks) that examined adverse effects in youths, weight gain was most prominent in olanzapine (~20 lbs), clozapine, quetiapine and risperidone recipients; aripiprazole was the most weight neutral.[11-14] Such weight gain persists during long-term treatment.[15] Clozapine and

[*] A treatment visit is defined as a visit that was concluded with a prescription being issued.

olanzapine also consistently elevate fasting glucose, insulin and triglycerides.[16] Based on limited comparative data, cholesterol is increased most significantly by olanzapine, quetiapine and risperidone, and triglycerides also are increased by risperidone; the latter also is most likely to increase prolactin levels.[11-14] Children and adolescents may be more sensitive than adults to metabolic changes occurring during long-term treatment, especially weight gain, total cholesterol, and triglycerides.[17] Weight gain may be more likely in autistic children and in those with disruptive behavioral disorders.[18]

Increases in treatment-related adiposity predict insulin resistance. One retrospective analysis indicated that the risk of diabetes may be 4-fold higher in children 5 to 18 years of age who initiated therapy with atypical antipsychotic drugs between 2001 and 2008.[19] The risk of incident diabetes appears higher for users of clozapine and olanzapine.[20] The reported occurrence of EPS has been variable. Although these occur at lower frequencies than in patients treated with conventional antipsychotic drugs, the atypical agents most likely to be associated with EPS are risperidone and olanzapine, and in one study ziprasidone.[21] Atypical antipsychotics also are generally associated with an increased risk of somnolence and sedation.

SYSTEMATIC REVIEWS

Two recent systematic reviews are relevant. The Drug Effectiveness Review Project (DERP) is an Oregon-based collaboration of public and private organizations, including fifteen states, that have joined together to provide systematic evidence-based reviews of the comparative effectiveness and safety of drugs in many widely used drug classes and to apply the findings to inform public policy and related activities. DERP has conducted an ongoing drug class review of the atypical antipsychotic drugs. The most recent update was published in July 2010.[4] With respect to off-label uses, compared with placebo, risperidone, aripiprazole, and olanzapine improved behavioral symptoms in children and adolescents with pervasive developmental disorders, and risperidone and quetiapine showed efficacy in children and adolescent with disruptive behavior disorders.

Additionally, the Agency for Healthcare Research and Quality commissioned a comparative effectiveness review of the off-label use of atypical antipsychotics.[22] This review evaluated the use of atypical antipsychotics in children (younger than 12 years old) and adolescents (12 to 17 years old) with eating disorders (including anorexia nervosa and bulimia), attention deficit hyperactivity disorder, Tourette syndrome, and insomnia. Evidence of efficacy was noted for risperidone in the treatment of ADHD and Tourette syndrome, while quetiapine and olanzapine were not effective in the treatment of anorexia nervosa, and risperidone was not effective in managing insomnia. These commissioned reviews and the Cochrane library (www.thecochranelibrary.com) are good sources for other systematic reviews on atypical antipsychotic drugs.[4,22]

PRACTICE GUIDELINES

In 2011, AACAP developed a practice parameter for clinicians on the use of atypical antipsychotics in children and adolescents.[1] A previous practice parameter from AACAP on the assessment and treatment of children and adolescents with bipolar disorders also is germane.[23] The former, which covered the literature to 2010 offers guidance on the clinical use of atypical antipsychotics in pediatric patients based on 19 separate recommendations. These recommendations address:

- Principles inherent in using psychotropic medication in children and adolescents;
- Risks associated with these drugs, including recommended history taking, baseline assessments, duration of therapy, and discontinuation;
- Dosing recommendations based on disease target and attendant side effects;
- Issues with the use of multiple psychotropic medications;
- Recommendations for safety monitoring especially weight, body mass index, heart rate, blood pressure, electrocardiogram, blood glucose, and lipid profiles;
- Measurements of movement disorders using structured measures; and
- Drug specific risks.

The reader is referred to the AACAP practice parameter for further information and specific clinical practice recommendations.[1]

Evidence-based recommendations for monitoring the safety of atypical antipsychotics in children and adolescents also have been developed by the CAMESA Guideline Project.[2] These recommendations address the first six atypical antipsychotics that were approved in the U.S. and exclude the newer agents paliperidone, asenapine, iloperidone, and lurasidone. Monitoring recommendations address height, weight, BMI, waist circumference, blood pressure, EPS, fasting blood glucose, insulin, lipid profiles, liver enzymes, prolactin, and thyroid stimulating hormone. The same group also developed clinical advice for addressing emergent metabolic complications associated with the use of atypical antipsychotics in pediatric patients.[3] Treatment recommendations addressed minimizing weight gain and managing abnormal BMI, waist circumference, blood pressure, fasting blood glucose, insulin, lipid profiles, liver function tests, TSH, and prolactin levels.[3]

DISCUSSION

Although certain atypical antipsychotic drugs are FDA-approved for specific uses in pediatric patients, the majority of prescribing (70 to 75%) is off-label for these drugs. Head-to-head comparisons of atypical antipsychotic drugs for off-label uses are few, and evidence from placebo-controlled trials for off-label use suggests that efficacy differs between drugs. Accordingly, one cannot anticipate that a "class effect" exists for atypical antipsychotics with respect to any specific clinical use or indication.

Little evidence exists on how treatment efficacy varies among populations, including how clinical responses may be influenced by sex, race, ethnicity, or medical co-morbidities. The metabolic effects of atypical antipsychotics are concerning. Because the risk of childhood obesity is inversely related to socioeconomic status, low-income children who are already at high risk for obesity and related metabolic disorders may be especially vulnerable to the adverse effects of weight gain from atypical antipsychotics.[24]

Improving Health Outcomes

In order to improve outcomes in pediatric patients who are candidates for treatment with atypical antipsychotics, treatment must include appropriate baseline assessments, examination of risks and benefits, adequate ongoing monitoring of key metabolic and neurologic variables, and management of emergent metabolic and physiologic conditions. Clinical guidance is available from AACAP and CAMESA. Nothing in the recently published literature significantly affects the basis from which these recommendations were derived; however, additional study, especially further long term measures of safety and efficacy would be helpful to inform clinical decision-making.

RECOMMENDATIONS

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

That our AMA:

1. Urge the National Institute of Mental Health to assist in developing guidance for physicians on the use of atypical antipsychotic drugs in pediatric patients.

2. Encourage and support ongoing federally funded research, with a focus on long term efficacy and safety studies, on the use of antipsychotic medication in the pediatric population.

3. Rescind Policy D-120.955 as it has been accomplished by preparation of this report.

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Table. Atypical Antipsychotic Drugs Marketed in the United States

Generic Name	Trade Name
Aripiprazole	Abilify®
Asenapine	Saphris®
Clozapine*	N/A
Iloperidone	Fanapt®
Lurasidone	Latuda®
Olanzapine*	Zyprexa®
Paliperidone	Invega®
Quetiapine*	Seroquel®
Risperidone*	Risperdal®
Ziprasidone	Geodon®

*Available as a generic equivalent

2. NATIONAL DRUG SHORTAGES-UPDATE

Reference committee hearing: see report of Reference Committee K.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS AND REMAINDER OF REPORT FILED
See Policy H-100.956.

INTRODUCTION

Recommendation 6 in Council on Science and Public Health Report 7-A-12, adopted as amended, directed the Council to continue to evaluate the drug shortage issue and report back on progress made in addressing drug shortages at the 2012 Interim Meeting of the House of Delegates.[1] Accordingly, this report provides an update on the current status of drug shortages, describes new developments, summarizes relevant American Medical Association (AMA) activities, and updates AMA policy on this issue.

CURRENT DRUG SHORTAGE INFORMATION

As of August 31, 2012, the Drug Shortages Management Resource Center maintained by the American Society of Health-System Pharmacists (ASHP) identified 214 existing drug shortages.[2] According to the Drug Information Service at the University of Utah, which provides information to the ASHP Resource Center, 123 new drug shortages occurred in 2012 as of August 31. This represents approximately a 33% decrease compared with the same time period in 2011. The Food and Drug Administration (FDA) drug shortages website identified 115 existing shortages of "medically necessary drugs" and 54 resolved drug shortages.[3] Existing shortages of medically necessary drugs are down approximately 5% from May 2012. The list maintained by ASHP is more comprehensive than the FDA list in that a "medically necessary" filter is not applied. The primary product category in short supply continues to be generic sterile injectables.

LEGISLATIVE AND REGULATORY ACTIONS

Passed by Congress on June 27th and signed into law by President Obama on July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) reauthorized user fees for prescription drugs, biological products, and medical devices and extended this concept to generic drugs for the first time.[4] User fees account for a majority of the FDA's annual budget. These fees are dedicated to expediting the drug and device development process and FDA review of applications, including post-marketing safety activities.

FDASIA contained numerous other provisions including Title X-Drug Shortages. Several recommendations previously offered by the Council to address drug shortages were reflected in Title X. Provisions intended to address drug shortages included the following:

- Require manufacturers of drugs that are "life-supporting, life-sustaining, and intended for use in the prevention or treatment of a debilitating disease or condition, including those used in emergency medical care or surgery" to notify the FDA 6 months in advance (or as soon as possible) if manufacturing is going to be "interrupted" or

discontinued. This provision codifies what has been a voluntary, but helpful, practice in helping the FDA to mitigate drug shortages. This provision is aligned with AMA Policy H-100.956(2) (see Appendix).

- Give the Secretary authority to expedite establishment inspections and review of supplements and applications (including of biological products) that could help mitigate or prevent a "shortage." This provision is aligned with Policy H-100.956(3).
- Require the Secretary to establish a task force to enhance the Secretary's response to shortages, and create a strategic plan to address stated aspects of shortages. This provision is aligned with Policy H-100.956(4).
- Require FDA to maintain a drug shortage list and provide patients, providers, and the public with such information in order to prevent, mitigate, and manage drug shortages on the ground. Safeguards are included that would "prevent the release of confidential business information or information that could adversely affect public health." What might constitute information adversely affecting public health was not specified or further explained.
- Require the Drug Enforcement Administration (DEA) to provide timely approvals or denials of increases in quotas of controlled substances in instances where such an increase could help address a drug shortage. Also, require DEA to report annually on their efforts to address drug shortages based on metrics established by Congress. This provision is aligned with Policy H-100.956(9).
- Allow hospitals within the same health system to repackage drugs into smaller units to alleviate drug shortages.
- Authorize the Government Accountability Office to conduct a study to examine the causes of drug shortages and issue recommendations on how to prevent or alleviate a drug shortage. This provision would provide needed data on how the regulatory framework, manufacturing challenges, economic factors, or other factors contribute to drug shortages. This provision is aligned with Policy H-100.956(7).

INDUSTRY INITIATIVES

The Generic Pharmaceutical Association's (GPhA) proposal to address shortages by having generic manufacturers share production information for drugs in short supply with FDA through a third party was endorsed by the Federal Trade Commission.[5] Under the Accelerated Recovery Initiative, IMS Health will collect information from manufacturers on real time supply and distribution information, as well as projected production and release forecasts. IMS will use this information along with market data, to analyze whether, and to what extent, the anticipated supply of a given drug is likely to fall short of the projected demand over the next several months. IMS will then share this information with the FDA to head off potential drug shortages. The FDA, with input from GPhA, will decide on the initial group of drugs to be addressed through this initiative.

CONGRESSIONAL REPORTS

Committee on Oversight and Government Reform

Just prior to HOD deliberations at A-12, the U.S. House of Representatives Committee on Oversight and Government Reform released a staff report that was critical of the FDA, concluding that the agency's action had contributed significantly to the drug shortage crisis.[6] The report blamed the agency for enforcement and regulatory actions, including a surge in warning letters that shut down a substantial amount of manufacturing capacity and/or placed facilities into remediation. The FDA vigorously defended its activities and in a point-counterpoint fashion rebutted most of the report's findings and conclusions.[7] The Committee's report also concluded that the reimbursement formula for injectable drugs in outpatient settings under Medicare Part B was a significant contributing factor.

U.S. Senate Committee on Commerce, Science, and Transportation

The U.S. Senate Committee on Commerce, Science, and Transportation held a hearing on July 25, 2012, examining the so-called "gray market" drug companies that drive up the cost of short-supply prescription drugs. The hearing and accompanying report explored how and why hospitals and other health care providers sometimes struggle to obtain short-supply prescription drugs they need to treat patients suffering from cancer and other life-threatening conditions.[8] The sale and distribution pedigrees of 5 sample drugs in short supply revealed that such drugs leaked out of authorized distribution channels into the gray market supply chain from pharmacies 69% of the time. On average the drugs passed through 3 to 4 different gray market businesses before finding their way into a hospital pharmacy, with substantial markups at each stop in the distribution chain.

ECONOMIC/REIMBURSEMENT FACTORS

Recommendation 10 in CSAPH Report 7-A-12, offered by the reference committee and adopted by the HOD, urged that Congress amend the 2003 Medicare Modernization Act (MMA) to allow for more reasonable payment rates for prescription drugs.[1] While this act cannot actually be amended, as noted in Policy H-100.956 (10), the intent was to have Congress re-examine the current reimbursement formula for injectable drugs administered on an outpatient basis under Medicare Part B. The MMA substantially reduced payment rates for chemotherapy drugs administered on an outpatient basis starting in January 2005. Currently, Medicare reimburses physicians the average sale price (ASP) plus 6% to cover the cost of administering injectable drugs. Increases are limited to a maximum of 6% every six months.

For the past several years, the AMA along with a number of impacted medical specialties such as oncology, have expressed concern that the ASP + 6 percent formula has resulted in persistent under-reimbursement that impacts small physician practices, in particular. The method for calculating ASP includes discounts and rebates that hospitals, large practices, and group purchasing organizations (but not small practices) are able to negotiate. Accordingly, small practices have to administer some treatments at a loss or refer their patient elsewhere. This undermines continuity of care at a critical time for patients and leads to fragmentation of care which carries increased costs. Ultimately, the foregoing hinders efforts to improve patient outcomes.

These problems have been further exacerbated by the persistent shortages that have emerged since the Part B payment policy change. The vast majority of the drugs in short supply are physician administered generic sterile injectable drugs, including cancer drugs, anesthetics for surgery, drugs for emergency medicine, and electrolytes for intravenous feeding. Although some proposals have suggested the ASP formula contributes to drug shortages, no consensus has emerged that raising the ASP formula (or changing the metric to use average wholesale prices instead) would lessen drug shortages because of other complexities in the drug distribution chain.

An economic analysis conducted by the U.S. Department of Health & Human Services Office of the Assistant Secretary of Planning and Evaluation (ASPE) concluded that increasing the production capacity for generic sterile injectable drugs was the single most important solution to the drug shortage crisis.[9] Between 2006-2010, while the overall market for sterile injectable oncology drugs increased by 14%, the overall generic sterile injectable market (including both oncology and other products) expanded by 52% fueled, in part, by a large increase in the number of abbreviated new drug applications (>300) that were approved in 2008-2010. While not claiming a direct cause and effect relationship, the report also noted average prices declined annually among oncology drugs that eventually experienced a shortage between 2008 and 2011. The average prices of drugs that never experienced a shortage over this period did not change or increased slightly. A report from IMS noted that a segment of drugs on the shortage list exhibited declining sales in 2010-2011 compared with the base period of 2006-2009; a smaller percentage was stable; and about 20% experienced growing volume sales (over 3-fold since 2006).[10] For those in the declining category, monthly supply fell an average of 47% over the five-year period.

In contrast to the ASPE report, the IMS report found that the average annual price per standard unit varied significantly across these three segments but not in a consistent way. Finally, a recent analysis of the MMA policy changes that prompted a reduction of Medicare Part B reimbursements for physician administered generic drugs provides some evidence that the policy change may, in fact, be at least one significant contributing factor for shortages of Part B generic drugs.[11] One intermediate solution would be to not include discounts and rebates in the calculation of ASP. Other new payment strategies that are being tested today include a “clinical pathways” approach that rewards oncologists for compliance with predetermined chemotherapy regimens and bundled or episode payment approaches. Both are focused on improving patient outcomes.[12,13]

CONCLUSION

Drug shortages continue to exact a toll on clinical practice and patient outcomes; only small gains have been made in the extent of the problem. No quick fix is evident, but recent legislative actions may help foster continued improvements that can be achieved by early notification of problems allowing for expedited solutions. The current shortages will “likely be resolved when new supply sources come on line as the manufacturing industry increases its capacity.”[9] In the meantime, voluntary collaborative efforts in the most severely stressed part of the industry (generic sterile injectables) may help to stabilize at least a segment of that market. Some focus on increasing the

extent of supply responsiveness in the market also is needed. Further root cause analysis may help inform additional solutions.

RECOMMENDATION

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

That Policy H-100.956 be amended by insertion and deletion in sections 6 and 10 to read as follows:

6. The Council on Science and Public Health will continue to evaluate the drug shortage issue and report back on progress made in addressing drug shortages at the ~~2012 Interim Meeting of the House of Delegates~~ 2013 Annual Meeting.

10. Our AMA will collaborate with medical specialty partners in identifying and supporting legislative remedies that ~~urges Congress to amend the 2003 Medicare Modernization Act to~~ allow for more reasonable and sustainable payment rates for prescription drugs.

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APPENDIX - Policy H-100.956, National Drug Shortages

1. Our AMA supports the recommendations of the 2010 Drug Shortage Summit convened by the American Society of Health System Pharmacists, American Society of Anesthesiologists, American Society of Clinical Oncology and the Institute for Safe Medication Practices and work in a collaborative fashion with these and other stakeholders to implement these recommendations in an urgent fashion.
2. Our AMA supports requiring all manufacturers of Food and Drug Administration approved drugs and, including FDA approved drugs with recognized off-label uses, to give the agency advance notice (at least 6 months prior or otherwise as soon as practicable) of anticipated voluntary or involuntary, permanent or temporary, discontinuance of the manufacture or marketing of such a product.

3. Our AMA supports authorizing the Secretary of Health and Human Services to expedite facility inspections, and the review of manufacturing changes, drug applications and supplements that would help mitigate or prevent a drug shortage.
4. Our AMA supports the creation of a task force to enhance the HHS Secretary's response to preventing and mitigating drug shortages and to create a strategic plan to: (a) enhance interagency coordination; (b) address drug shortage possibilities when initiating regulatory actions (including the removal of unapproved drug products from the market); (c) communicate with stakeholders; and (d) consider the impact of drug shortages on research and clinical trials.
5. Our AMA will advocate that the U.S. Food and Drug Administration and/or Congress require drug manufacturers to establish a plan for continuity of supply of vital and life-sustaining medications and vaccines to avoid production shortages whenever possible. This plan should include establishing the necessary resiliency and redundancy in manufacturing capability to minimize disruptions of supplies in foreseeable circumstances including the possibility of a disaster affecting a plant.
6. The Council on Science and Public Health will continue to evaluate the drug shortage issue and report back on progress made in addressing drug shortages at the 2012 Interim Meeting of the House of Delegates.
7. Our AMA urges the development of a comprehensive independent report on the root causes of drug shortages. Such an analysis should consider federal actions, the number of manufacturers, economic factors, including federal reimbursement practices, as well as contracting practices by market participants on competition, access to drugs, and pricing.
8. Our AMA urges that procedures be put in place: (1) for the FDA to monitor the availability of Schedule II controlled substances; (2) for the FDA to identify the existence of a shortage that is caused or exacerbated by existing production quotas; and, (3) for expedited DEA review of requests to increase aggregate and individual production quotas for such substances.
9. Our AMA urges regulatory relief designed to improve the availability of prescription drugs by ensuring that such products are not removed from the market due to compliance issues unless such removal is clearly required for significant and obvious safety reasons.
10. Our AMA urges Congress to amend the 2003 Medicare Modernization Act to allow for more reasonable payment rates for prescription drugs. (CSAPH Rep. 2, I-11; Modified: CSAPH Rep. 7, A-12)

3. RISK EVALUATION AND MITIGATION STRATEGIES

Reference committee hearing: see report of Reference Committee K.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AND REMAINDER OF REPORT FILED
See Policy H-100.961.

INTRODUCTION

Policy D-100.971 directs the American Medical Association (AMA) to work with the pharmaceutical and biological industries to increase physician awareness of risk evaluation and mitigation strategies (REMS) as a means to improve patient safety. The Council previously addressed the issue of REMS in Council on Science and Public Health Report 8-A-10.[1] By providing an update of REMS programs in the U.S., this report can serve as a contemporary resource for helping to increase physician awareness of this issue.

METHODS

Information for this report was largely based on information gleaned from ongoing staff drug policy activities, the internet sites of the U.S. Food and Drug Administration, and the REMS tracker maintained by the law firm of Hyman, Phelps, and McNamara.

WHAT IS A REMS

A REMS is a risk management plan that uses risk minimization strategies beyond professional product labeling; it can be required before approval if the FDA determines a REMS is needed to ensure that the benefits outweigh the risks of the drug, or it can be required post-approval if new safety information emerges that requires use of this approach to keep the drug on the market. Manufacturers are accountable for development of the REMS program, certification and education of physicians, collection of performance and outcomes data, as well as surveillance and assessment of program effectiveness. FDA authority to require a REMS was vested in the 2007 Food and Drug Administration Amendments Act (FDAAA).[2] A REMS can include: (1) medication guide or patient package insert; (2) communication plan for health care practitioners; and (3) elements to ensure safe use.[2] As designed, a REMS

also includes an implementation system, a sponsor's plan to assess the performance of the REMS, and a timetable for assessment.

Medication guides may be required if FDA determines that patient awareness of serious risk(s) could affect their decision to use the product, information in the guide could help prevent serious adverse effects, or the drug product is important to patient health and patient adherence to directions for use are critical to the drug's effectiveness.[3] Medication guides or patient package inserts are provided to the patient at the point of dispensing. These are distinct from the patient medication information (PMI) sheets or leaflets that are typically dispensed with other prescription drug products and that vary depending on the pharmacy and vendor used to create them.[4] Medication guides are widely viewed as a poor solution to mitigating risk and/or promoting appropriate and safe drug use. They are written at a literacy level that is too high and present risk information that may confuse patients or result in actual refusal to take needed medications. The entire PMI framework is under review, and the FDA has begun moving toward a so-called "single document" solution for written patient information to improve communication of both benefit and risk information to the patient in a manner that promotes understanding and improves adherence in an appropriate way.

Originally, medication guides were an integral component of virtually all REMS programs. Between the time when the REMS provision of FDAAA took effect and January 1, 2011, FDA approved more than 150 medication guides as part of a REMS; more than 70% of these REMS were based on the medication guide only. Subsequently, the FDA issued Guidance[5] that outlined a procedure for sponsors to request removal of medication guides from REMS. Based on this procedure and decisions that some REMS are no longer required to ensure patient safety, more than 100 REMS have been "retired." In most cases moving forward, the FDA expects to include a medication guide as part of REMS only when the REMS includes elements to ensure safe use.

Elements to Ensure Safe Use (Restricted Distribution)

Currently, of greatest concern to physicians are those drugs with REMS that include so-called "elements to assure safe use"[2] (ETASU), also referred to as restricted distribution. Elements to ensure safe use include the following general categories.[2] They are not mutually exclusive and in fact considerable overlap may exist for individual products.

- Physicians who prescribe the drug must be certified or undergo specialized training;
- Retail pharmacies or other dispensers (specialty/central pharmacies) of the drug must be certified or the drug is available only from a single central pharmacy;
- Dispensing/administering the drug is allowed only in limited healthcare settings (e.g., sites equipped to treat adverse reactions);
- The drug can be dispensed/administered only with evidence of safe use conditions (e.g., dispensing the drug only after qualifying laboratory test results; patient undergoes specific informed consent or is enrolled in specific program; drug dispensed by special courier; patient must already be opioid-tolerant);
- Each patient using the drug is subject to certain monitoring or required benefit-risk assessment; and
- Prescribers, pharmacies, and/or treated patients must be enrolled in a registry.

Currently Approved REMS

As of August 14, 2012, REMS were approved for 69 products as follows:[6,7]

- 19 REMS with medication guides only;
- 22 REMS included a communication plan only;
- 9 REMS included a medication guide and a communication plan;
- 26 individual REMS included ETASU (most of these also include a medication guide and communication plan).

In addition, three currently approved single shared system REMS exist: (1) isotretinoin (IPLEDGE; six different generic manufacturers); (2) transmucosal immediate-release fentanyl products (sublingual tablets and spray, transmucosal lozenge, buccal tablets and film, and nasal spray formulations); and (3) long acting opioids (long-acting/extended release opioid drugs, oral methadone, and transdermal fentanyl products). A few drugs (clozapine, smallpox vaccine, sodium oxybate) still exist that were approved with restricted distribution programs prior to FDAAA and creation of the REMS framework. Such products are "deemed" to have a REMS but do not appear on the FDA's list of approved REMS.[8]

Working with Industry

The AMA has demonstrated its commitment to working with industry on the opioid REMS by providing public commentary, participating in stakeholder meetings of the industry working group, and expressing a willingness to participate in the voluntary education of physicians on the safe and effective use of long-acting opioid products.

COMMENT

While the FDA does not have the authority to regulate physicians, its decisions and actions on REMS and other risk management approaches affect the daily practice of medicine. Physicians are responsible for implementing certain aspects of REMS in their practices, and as the number of REMS with ETASU continues to increase, it seems clear that such REMS have the potential to affect patient access. The lack of uniformity among ETASU and the possible competing or conflicting nature of ETASU are onerous administrative burdens physicians face at the same time they are obligated to meet other administrative and clinical requirements of private and public insurance companies, such as prior authorization, step therapy, obtaining off-formulary drugs through an appeals process for their patients, and supporting patient assistance programs.

To meet some REMS requirements, physicians must spend additional time on administrative tasks associated with registration, training and certification, and documentation. This detracts from the time that is needed for diagnosis, patient discussion, and the design and implementation of a treatment plan that is acceptable to the patient. Furthermore, the multiplicity of programs requiring separate informed consent forms, enrollment, certification, or attestation are primarily paper-based and have not evolved with the architecture of electronic medical records and e-prescribing, which contributes to further disruption in workflow and patient care. Patient safety is of paramount importance to physicians; however, strategies to ensure the safe use of prescription drugs need to be evidence-based and administratively simple in order to succeed.

Of equal, and perhaps greater concern, is the trend for prescriber training becoming a key element of risk management for prescription drugs. Recently, the FDA approved the first drug for the prevention of sexually transmitted HIV infections (emtricitabine plus tenofovir, Truvada®) with a REMS program that includes prescriber training and education. This comes on the heels of the approval of a new weight loss drug (phentermine plus topiramate, Qsymia™) which requires prescriber training, as well as pharmacy certification. FDA's push to include more educational programs, including verification of completion of such training, could suggest an expanded role for continuing medical education (CME) as part of the REMS process. Such an approach is an integral element of the class-wide opioid REMS program, although the education in this instance is voluntary. Using industry-funded CME as a centerpiece of mandatory prescriber training within a REMS program raises an entire set of additional concerns related to manufacturer and stakeholder involvement in the design of such programs, enforcement, program integrity and administrative burdens.

Current AMA policy remains relevant in seeking to have the FDA establish a procedure for physician and other stakeholder involvement early in the REMS development process, standardizing the REMS processes, creating REMS that are patient-centric, and establishing methods and metrics to assess the impact of ETASU on clinical practice and health outcomes.

RECOMMENDATION

The Council on Science and Public Health recommends that Policy H-100.961, The Evolving Culture of Drug Safety in the United States: Risk Evaluation and Mitigation Strategies (REMS), be amended by insertion and deletion to read as follows and the remainder of the report be filed.

(1) The Food and Drug Administration (FDA) issue a final industry guidance on Risk Evaluation and Mitigation Strategies (REMS) with provisions that: (a) urge ~~require~~ sponsors to consult with impacted physician groups and other key stakeholders early in the process when developing REMS with elements to assure safe use (ETASU); (b) establish a process to allow for physician feedback regarding emerging issues with REMS requirements; and (c) recommend ~~clearly specify~~ that sponsors ~~must~~ assess the impact of ETASU on patient access and clinical practice, particularly in underserved areas or for patients with serious and life threatening conditions, and to make such assessments publicly available. ~~;and (d) conduct a long-term assessment of the prescribing patterns of drugs with REMS requirements~~.

(2) The FDA, in concert with the pharmaceutical industry, evaluate the evidence for the overall effectiveness of REMS with ETASU in promoting the safe use of medications and appropriate prescribing behavior.

(~~2~~3) FDA ensure appropriate Advisory Committee review of proposed REMS with ETASU before they are finalized as part of the premarket review of New Drug Applications, and that the Drug Safety and Risk Management Advisory Committee fulfills this obligation for drugs that are already on the market and subject to REMS because of new safety information.

(~~3~~4) To the extent practicable, a process is established whereby the FDA and sponsors work toward standardizing procedures for certification and enrollment in REMS programs, and the common definitions and procedures for centralizing and standardizing REMS that rely on ETASU are developed.

(~~4~~5) REMS-related documents intended for patients (e.g., Medication Guides, acknowledgment/consent forms) be tested for comprehension and be provided at the appropriate patient literacy level in a culturally competent manner.

(6) The FDA solicit input from the physician community before establishing any REMS programs that require prescriber training in order to ensure that such training is necessary and meaningful, requirements are streamlined and administrative burdens are reduced.

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4. CLINICAL APPLICATION OF NEXT-GENERATION GENOMIC SEQUENCING

Reference committee hearing: see report of Reference Committee K.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS AND REMAINDER OF REPORT FILED
See Policy H-460.905.

INTRODUCTION

In a 2010 report, the Council on Science and Public Health (Council) reviewed the increasing use of genomic-based technologies in clinical care.[1] With the advent of new DNA sequencing technologies, referred to as "next-generation sequencing," large-scale analysis of individual genomes has become possible and is rapidly being deployed to guide clinical care. Next-generation sequencing technologies have the potential to drive significant improvements in patient care and outcomes, yet concerns exist that will require careful consideration to ensure appropriate clinical implementation.

One of the Council's designated functions is to advise the American Medical Association (AMA) on substantial and promising developments in the scientific aspects of medicine and biomedical research. Accordingly, the Council initiated this report to briefly review the clinical applications of next-generation sequencing, concerns surrounding its implementation, and the extent to which the increasing accessibility of genomic data has the capability to improve health outcomes.

METHODS

Literature searches were conducted in the PubMed database for English-language articles using the search terms "next generation sequencing," "whole genome sequencing," and "whole exome sequencing," along with the terms "clinic," "clinical," and "physician." To capture reports that may not have been indexed on PubMed, a Google search was also conducted using the same search terms. Additional articles were identified by manual review of the references cited in these publications.

NEXT-GENERATION SEQUENCING TECHNOLOGY

In 1990, the U.S. embarked on an ambitious goal at the time, to sequence the entire human genome of approximately three billion base pairs.[2-4] The Human Genome Project took more than 10 years to complete and cost $2.7 billion,[5] but the sequence has been extraordinarily valuable to researchers studying the genetic causes of disease and to clinical applications that stem from such research. The length and cost of the Human Genome Project was primarily due to the DNA sequencing technology used at the time, called the Sanger method.[6] The Sanger method is highly accurate and is commonly used for sequencing small amounts of DNA, but it has limitations in its throughput capability.[7]

In anticipation that analysis of entire genomes would be valuable for clinical care, new sequencing technologies have been developed that enable rapid genome sequencing for dramatically reduced costs. These next-generation sequencing (NGS) technologies use "massively parallel" platforms that can sequence millions of DNA fragments simultaneously.[8,9] Using NGS, an entire individual genome can be sequenced in 2-3 days, and the cost has been decreased over 1700-fold, to less than $5000.[10-12] The cost is expected to decline well below $1000 in the near future, increasing individuals' interest in having their genome completely sequenced, and increasing the possibility that genome sequencing could become an affordable clinical tool.

Whole-Genome and Whole-Exome Sequencing

The decreased cost and increased speed of sequencing has made it reasonable to use large-scale genomic analyses as clinical tools. These NGS-based analyses include whole-genome sequencing (WGS) and whole-exome sequencing (WES). In WGS, genomic DNA is isolated from a patient's blood or tissue sample, and its sequence determined.[8] A software program then compares the patient's sequence to a reference sequence, notes differences, and then searches databases to determine which differences are clinically relevant.[8] These software programs are a necessity because of the large amount of data generated when a whole genome is sequenced.[9] In a typical person's sequence, WGS will reveal more than 3 million variants.[13-14] Even after data analysis programs have filtered out variants that do not appear to be clinically relevant, hundreds to thousands of variants could remain that may be the cause of disease.[9]

DNA sequences that encode proteins are called exons, and make up only approximately one percent of the human genome; the other 99 percent is made up of non-coding regulatory elements, RNA processing elements, and regions of unknown function. The large majority of disease-causing mutations, more than 85 percent, occur in exons.[14-16] WES examines the sequences of all of the exons in an individual, or the "exome." In WES, the exons are first isolated from the non-coding DNA, and then the sequences determined. Generally, about 20,000 variants are identified in each individual.[14] Like WGS, software programs sift through the sequence data to determine which variants are clinically meaningful. WES is less costly than WGS, and the exome represents a highly enriched subset of the genome in which to search for disease-causing variants, making the identification of clinically meaningful results somewhat more efficient. However, WGS has the potential to detect large chromosomal structural variants that WES often misses, like insertions and deletions, inversions, and translocations.[8] As sequencing costs continue to fall, it is likely that WES will be gradually replaced by WGS.[9]

WGS and WES have so far shown the most clinical utility in facilitating an accurate diagnosis in individuals with disorders that present with atypical manifestations, are difficult to confirm using clinical or laboratory criteria alone,

or require extensive or costly evaluation.[8,9,14,17] Complex disorders are often genetically heterogeneous, meaning that multiple variations may be causal, and in many cases, not all of the causal variants are known.[17] Complex disorders also tend to have broad presentations that are difficult to diagnose. Examples of such disorders are intellectual disability, sensorineural deafness, and mitochondrial dysfunction.[17] For a disorder with a suspected genetic cause, targeted testing of single candidate genes is usually most efficient in identifying the genetic cause of disease, but that approach is not possible when the presentation is too broad to identify candidate genes to test, or may be very expensive and inefficient if dozens of candidates are sequenced one by one.[9] In these situations, WGS/WES has been used to analyze the entire genome sequence, searching for any variation that may be causal of disease.[18-19]

Clinical application of WGS and WES. While WGS and WES are not yet routinely implemented, their potential utility in facilitating diagnosis and thereby guiding therapy has been demonstrated.[8,14,17-21] In these cases, diagnoses and effective treatments would not have been possible without the genomic data generated by WGS/WES.[18-22] In a number of cases, insurance companies have paid for WGS/WES, an acknowledgement that the tests are more effective in determining a diagnosis than sequencing individual candidate genes or other diagnostic procedures.[8]

In the most well known example of the clinical application of WES, physicians were unable to arrive at a definitive diagnosis for a young boy suffering from life-threatening inflammatory bowel disease, even after many months of hospitalization, comprehensive clinical evaluation, more than 100 surgeries including the removal of his colon, and targeted genetic analysis.[20] In an attempt to identify other causal mutations, WES was carried out and a mutation in the gene *XIAP* was identified. *XIAP* mutations are frequently associated with hemophagocytic lymphohistiocytosis, but had not been described as causative of bowel disease.[20] Based on the suggested treatment for XIAP deficiency, an allogeneic hematopoietic progenitor cell transplant was performed. Within weeks of the transplant, the boy was able to eat and drink, and at the time of case publication, had had no recurrence of his symptoms.[20]

WGS was used in a pair of fraternal twins diagnosed with dopa (3,4-dihydroxyphenylalanie)-responsive dystonia (DRD), and was critical in informing improved therapy. After several years of successful $_{L}$-dopa treatment, the twins' DRD symptoms were no longer well controlled, with tremors, unsteady gait, dystonia, and laryngospasms occurring.[19] Targeted genetic analysis did not detect mutations in the primary candidate genes for DRD, so WGS was undertaken to identify other causal mutations. A mutation in a gene encoding a cofactor for the production of both dopamine and serotonin was identified, leading to the recommendation that the serotonin precursor 5-hydroxytryptophan be added to the twins' therapeutic regimen.[19] At the time of case publication, both twins had shown marked improvement.[19]

These and other success stories of patients who, thanks to WGS/WES, have seen an end to years of severe symptoms and procedures without a diagnosis or therapy are illustrative of its potential to improve health outcomes.[8,17-22] Recent studies have provided evidence that a WGS/WES-based approach results in a diagnosis more accurately, quickly, and less expensively than using non-WGS/WES-based diagnostic procedures, and that it should be strongly considered in all cases in which a genetic condition is suspected but targeted genetic testing has proven negative.[21,23] Evidence also shows that WGS/WES often improves clinical management by revealing therapeutic options not previously considered, ruling out therapies that would not have been successful, or by guiding genetic counseling.[21]

Examining Cancer using Next-Generation Sequencing (NGS)

Cancer is a genetic disease caused by heritable and acquired mutations, so DNA sequencing is essential in detecting, managing, and treating the disease.[24] Tools that determine the molecular signature of tumors have been used for many years to aid in diagnosis and management decisions. In recent years, panel-based assays that detect dozens of variations in gene expression within tumors have been employed to profile breast tumors and predict prognosis and response to chemotherapy.[25,26] NGS has enabled a new generation of tests that rapidly analyze tumor DNA to detect hundreds of variants that may drive cell growth and reveal clues about what treatment options may be effective.[27-29]

NGS technologies have also enabled the rapid sequencing of the entire tumor genome, with the hope that variants can be identified to more precisely classify the tumor and choose tailored therapies. For example, in a woman whose clinical presentation was consistent with acute promyelocytic leukemia but whose cytogenetic results suggested a different subtype with poor prognosis and for which bone marrow transplantation is recommended, WGS of DNA extracted from the leukemic bone marrow was performed.[30,31] In comparing the DNA sequence of the leukemic cells to the sequence derived from a non-cancerous sample of the woman's tissue, a novel chromosomal translocation was

discovered that led to a change in therapy.[30] The woman was treated with retinoic acid and was no longer considered a candidate for bone marrow transplantation.[30,31]

WGS is increasingly being incorporated into oncology clinical research studies, and it is expected that translation from clinical research into oncology practice will shortly follow.[32] As panel-based expression assays shown to improve clinical management of cancer patients are being transitioned to NGS-based tests, analyses show that the NGS-based methods accurately detect the variants included in the expression panels, while also detecting more than 2,000 additional variants associated with tumor growth.[33] In another study, an NGS-based test revealed therapeutic options for more than three-quarters of patients with non-small cell lung cancer.[29]

Special challenges exist in the sequencing of tumor DNA. Cancer specimens tend to include necrotic or apoptotic cells that reduce the nucleic acid quality, and usually contain a mixture of malignant and non-malignant cells that exhibit cancer and non-cancer genomes, respectively.[34] Cancer genomes also tend to mutate at high frequencies causing clonal variation within the tumor.[34] However, techniques exist to address these challenges, and the potential for NGS methods to rapidly provide diagnostic and therapeutic information not possible with targeted analyses will drive its growth in clinical care.[34]

CHALLENGES TO CLINICAL INTEGRATION

The integration of NGS-driven technologies like WGS is inevitable,[35,36] but their potential to improve patient care is dependent on addressing challenges such as managing extremely large datasets, return of results, and regulation and reimbursement.

Managing Sequence Data

Older DNA sequencing methods have typically been the rate-limiting factor for the clinical use of genetic data. Prior to NGS methods, it was not possible to generate a whole genome sequence quickly enough for it to be of clinical value. As NGS methods continue to enable rapid WGS, the rate-limiting factor has shifted to one of data handling. The amount of sequence data contained in a whole genome is approximately 3 billion base pairs, or 6 million bases.[37] If one were to print the sequence in small font onto paper, it would result in a 400,000 page document.[37] The space needed to store the raw data file from only one whole genome exceeds the capability of most home computers.[38] Decreased cost and improvement in storage capability, as well as cloud-based storage, are expected to be solutions to the data storage problem.[39-41]

Once the 6 billion bases of an individual genome are sequenced and a data file generated, clinically important variants must be identified. In an average whole genome, 3-4 million variants will be detected, 30,000-50,000 of which will be located in the exons (protein-coding regions).[13] This number of possibly clinically-important variants is so large that software programs are required to determine the significance of each variant. These programs take into account factors such as the known association of the variant with disease, evolutionary conservation of the sequence, the change to the resulting protein, the patient's phenotype, comparison to reference sequences, and possible patterns of inheritance.[8,42] Even after software programs weed out variants that do not appear to have clinical significance, hundreds of significant variants may remain.[9] Additionally, software programs continually update their algorithms so that new research associating variants to disease is incorporated.[43] Under ideal circumstances, this implies that an individual's genome should be reanalyzed periodically to detect variants that may not have been initially classified as clinically important.

Physician-Specific Concerns

Improving the knowledge deficit. As WGS/WES becomes a tool to inform diagnostic and therapeutic decisions, physicians will need to be knowledgeable about the technology and the situations in which it may be beneficial. However, as noted in the Council's 2010 report on Genomic-Based Personalized Medicine, a genetics knowledge deficit exists among many physicians.[1] It is widely believed that genetics training in medical school and residency programs, and for practicing physicians, should be improved.[1,44] Research revealing the extent to which WGS will contribute to medical care, and how such information will be incorporated into the workflow of the physician, will inform educational programs.[45] Recommendations for medical school curricula that emphasizes genetics interpretive and communication skills have been made, along with genomics certification programs for non-geneticist

physicians.[17] An understanding of bioinformatics will also be essential for meaningful clinical use of NGS-based tests.

Genetic counseling and workforce. Given the complexity of results arising from WGS and WES, it is essential that a team of health care providers, including medical geneticists, specialists in the disease under consideration, pathologists, and genetic counselors, be involved in the discussion and decision about whether WGS/WES is appropriate for the clinical situation, the interpretation of results, and the communication of those results to the patient.[7,30,45,46] Topics that should be covered in genetic counseling prior to testing include basic genetics, inheritance patterns, types of variation, false-positive and -negative results, privacy concerns, and rights under the Genetic Information Nondiscrimination Act.[8] One of the most important topics to cover is the patient's desire to receive incidental or secondary findings, i.e., variants that are not related to the phenotype under investigation but that impact the patient's health. For example, WGS carried out to determine a diagnosis for a child exhibiting intellectual disability may reveal that he or she carries a variant in the gene *FAP*, dramatically increasing the risk of colorectal cancer. Estimates for the number of hours of genetic counseling needed to cover these topics prior to WGS or WES is 6-8 for each patient.[8] This represents a significant amount of direct patient contact, and raises concerns about whether genetics professionals (clinical and molecular geneticists and genetic counselors certified by the American Board of Medical Genetics or the American Board of Genetic Counseling) have the time to conduct this type of counseling, especially since this country is experiencing a shortage of such professionals.[1]

Return of incidental findings. Once WGS/WES is carried out, the health care provider team will need to analyze variants and choose which are clinically significant. Even with the help of software programs, a physician could be faced with the possibility of hundreds of variants that may affect his or her patient's health, and many hours of background research to determine the role of those variants in disease. Physicians and genetic counselors must also be aware of the patient's desire to receive incidental findings, and consent processes that inform patients about the possibility of finding such results and their choice to receive them, are essential.[36,47] The American College of Medical Genetics and Genomics (ACMG) is in the process of developing a list of gene variations and conditions that even if found incidentally, meet criteria for duty to inform patients; these include conditions that are well-understood and that have medical interventions that result in significant benefit.[48]

When a patient chooses to receive results on all variants considered clinically significant, the question arises as to what is considered "clinically significant." Most often, clinically significant applies to variants that are actionable, i.e., they lead to a change in care.[49] But debate exists about whether variants that lead to a diagnosis of disease that does not have an associated therapy are actionable.[47,49] The disease may not be treatable, but having a diagnosis may provide solace to the patient, prevent unnecessary diagnostic procedures, and afford the option of counseling about recurrence risk. When patients do choose to receive information on incidental findings, many hours of direct patient contact are needed to explain the variants.[36] For incidental findings that are considered actionable, confirmatory testing and other procedures will also be needed.

STANDARDS AND BEST PRACTICES

The many questions surrounding the appropriate clinical use of NGS technologies have prompted calls for the establishment of standards and best practices for both laboratories and physicians.[14,17] Members of the AMA Federation have been deeply involved in establishing policy and recommendations. The ACMG recently adopted policy recognizing that genomic sequencing approaches can be of great value in the clinical evaluation of individuals with suspected germ-line genetic disorders, but to maximize its utility, several key points should be considered.[50] For example, clinical situations in which WGS/WES may be valuable in the diagnostic assessment of an affected individual include: 1) when the phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available; 2) when a patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach; and 3) when a patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.[50] ACMG policy states that at this time WGS/WES is not appropriate for carrier or newborn screening, and that asymptomatic individuals interested in WGS/WES for screening purposes should seek out the guidance of a trained genetics professional.[50]

The College of American Pathologists (CAP) Personalized Health Care Committee and Emerging Technology team is currently identifying key policy drivers for the adoption of genomic medicine in a way that will maximize benefit

to patients. The CAP recently published a revised version of its molecular pathology checklist with a section on next generation sequencing (NGS) as part of the new edition of the CAP Laboratory Accreditation Program checklists.[51] The NGS section has 18 requirements that address the laboratory process and the subsequent bioinformatics analyses comprised of sequence alignment and mapping, variant calling, and annotation.[51]

REGULATION AND REIMBURSEMENT

Regulation of genetic tests is under the purview of both the Centers for Medicare and Medicaid Services and the FDA; a detailed description of the regulatory structure can be found in the Council's 2010 report.[1] Given the complexity and uncertainty in the current regulatory landscape, it is unclear whether NGS-based tests will be regulated differently than other genetic tests. Clinical laboratories will need to be proficient in performing NGS-based tests, implying that current laboratory certification requirements should be updated.[45] The CAP has already addressed this issue in the new edition of its Laboratory Accreditation Program Checklists.[51] Another component to consider is the software programs that categorize WGS/WES results as clinically significant or not, and in some cases, provide information on possible therapies. These software programs run on sophisticated algorithms and may themselves need to be regulated.[45] The AMA believes that any regulations put in place should preserve and enable physician discretion to provide, utilize and/or direct the use of the most appropriate diagnostic and treatment options.[52]

As the number of genetic tests grows rapidly and complexity increases, the ongoing need to regularly and swiftly update descriptive CPT codes, used for billing purposes, is clear. For several years, providers and laboratories have used "stacking codes" to describe molecular diagnostics, which only identified the procedures involved in the test process, not the test itself. Over the last 10 years, the AMA has been incrementally updating the coding system for molecular diagnostics diagnostics to keep pace with the rapid evolution of this technology. As a result of this effort, more than 100 codes that are analyte-specific and that specifically describe the most commonly-ordered genetic tests have been introduced.[53] It also assigned less commonly performed molecular pathology services to one of nine codes based on the level of resources required for their performance and interpretation.[53] A detailed description of the work can be found in the Appendix.

The rapid growth of NGS-based tests demonstrates the challenge for the iterative, evidence-based CPT process in keeping up with the technology. It is believed by some that even the newest molecular pathology codes do not adequately describe the complexity of NGS-based tests, and other entities have developed their own coding systems to fill this perceived gap.[54-56] Additionally, the Association for Molecular Pathology recently announced that it was finalizing a framework proposal for CPT coding of NGS-based assays.[57] Moving forward, it will be important for the AMA to continue expansion of its process for convening a wide array of stakeholders, and to adapt and remain agile enough to address rapid uptake of new technologies while still maintaining the rigor, transparency, and integrity of the current evidence-based process.

Questions remain about how health care providers will be reimbursed for pre-test counseling, the time spent interpreting the vast amounts of data received from WGS/WES sequencing, and the increased patient contact needed to fully explain the variants discovered.[36]

CONCLUSIONS

NGS-based technologies have the potential to drive significant improvements in patient care. Already WGS and WES have shown remarkable ability to end the diagnostic odyssey for patients with disorders that are resistant to standard diagnostic procedures and targeted genetic testing. Cancer patients also stand to gain from improved molecular analysis that enables accurate tumor classification, and improved diagnosis and management options. Current challenges to implementation must be addressed in order to fully realize the incredible potential of NGS-based technologies to improve health outcomes.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following recommendations be adopted and the remainder of this report be filed:

1. Our American Medical Association recognizes the utility of next-generation sequencing (NGS)-based technologies as tools to assist in diagnosis, prognosis, and management, and acknowledges their potential to improve health outcomes.

2. Our American Medical Association encourages the development of standards for appropriate clinical use of NGS-based technologies and best practices for laboratories performing such tests.

3. Our American Medical Association will monitor research on and implementation of NGS-based technologies in clinical care and will work to inform and educate physicians and physicians-in-training on the clinical uses of such technologies.

4. Our American Medical Association will support regulatory policy that protects patient rights and confidentiality and enables physicians to access and use diagnostic tools, such as NGS-based technologies, that they believe are clinically appropriate.

5. Our American Medical Association will continue to enhance its process for development of CPT codes for evolving molecular diagnostic services, such as those that are based on NGS; serve as a convener of stakeholders; and maintain its transparent, independent, and evidence-based process.

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APPENDIX - Improvements to CPT coding for molecular diagnostic tests

From 1998 to 2011, providers and laboratories have used "stacking codes" to describe molecular diagnostics, which only identified the discrete procedures involved in the test process (nucleic acid isolation, amplification, sequencing, etc.), not the test itself or the disease/condition that it was assaying. This stacking code methodology made comparisons across laboratories and aggregation of data difficult, and health plans often ended up developing their own identifiers for stacked code sets.[54] The AMA recognized this difficulty, tracked these test methodologies as the rapidly-growing technology matured, and conducted an assessment of the most clinically significant services. In response to the need for greater specificity and as a result of a stakeholder engagement process, in 2005, a new appendix of disease/condition-specific modifiers was added to the CPT code set, enabling payer identification of the disease/condition on claims in which the stacking codes were used. This represented an interim solution to the expected growth of molecular genetics in clinical practice over the next decade, enabling linkage of the stacking codes to the conditions/reasons for testing and distinct identification of 260 of the known potential combinations at that time. It also enabled the technology to mature before adding more granular molecular pathology codes.

To improve the coding system for molecular diagnostics, and after implementation of a relatively brief but intensive stakeholder process that began in 2009, the AMA in 2011 introduced a new set of more than 90 molecular pathology CPT codes that are analyte-specific and that specifically describe the most commonly-ordered genetic tests (Tier I codes).[53] The AMA also assigned less commonly-performed molecular pathology services to one of nine codes based on the level of resources required for their performance and interpretation (Tier II).[53] The CPT panel has also issued Multianalyte Assays with Algorithmic Analyses (MAAA) codes for procedures that utilize multiple results derived from assays of various types, including molecular pathology assays, fluorescent in situ hybridization assays and non-nucleic acid based assays (e.g., proteins, polypeptides, lipids, carbohydrates), and that are typically unique to a single clinical laboratory or manufacturer. Algorithmic analyses use the results of thee assays and sometimes other patient information to report a numeric score or probability that can determine diagnosis and/or therapy. In May 2012, the Association for Molecular Pathology (AMP) announced it was finalizing a framework proposal for CPT coding of Next Generation Sequencing (NGS)-based assays.

5. AMA POLICY CONSOLIDATION: INFLUENZA AND INFLUENZA VACCINE

Reference committee hearing: see report of Reference Committee K.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AND REMAINDER OF REPORT FILED
See Policies H-440.846, H-440.847, H-440.848, H-440.849, H-440.850 and H-440.851.

INTRODUCTION

This report is a Council on Science and Public Health initiative to consolidate several current policies of our American Medical Association (AMA) on issues related to the supply, distribution, payment, pandemic preparedness, and clinical recommendations for the use of influenza vaccine. As a whole, these policies seek to support efficient delivery and appropriate use of influenza vaccine in order to protect the health of the public and improve health outcomes. Consolidation will facilitate use of these policies by advocates in and outside of our membership.

Consolidation of several policies is influenced by the fact that they endorse recommendations from the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP). The ACIP recommendations pertaining to influenza vaccination were changed in 2010 to reflect an approach to universal vaccination as follows:

Routine annual influenza vaccination is recommended for all persons aged ≥6 months. To permit time for production of protective antibody levels, vaccination optimally should occur before onset of influenza activity in the community. Therefore, vaccination providers should offer vaccination as soon as vaccine is available. Vaccination should be offered throughout the influenza season (i.e., as long as influenza viruses are circulating in the community).

This recommendation represents a substantive change from the previous policy that focused on identifying and prioritizing the immunization of persons at high risk for complications from influenza.

As stated in Policy G-600.111, the purpose of policy consolidation is to make information on AMA policy more accessible. Policy consolidation also will improve the organization of the AMA policy database. The purpose of policy consolidation does not include the establishment of new policy positions. Consequently, Policy G-600.111 states that the recommendations in policy consolidation reports cannot be amended and must be voted upon in their entirety. Changes in AMA policy can be accomplished through other types of reports or by resolutions that are submitted to the AMA House of Delegates.

This report consolidates 15 policies from Section 440–Public Health of the AMA policy database. The Council proposes that the consolidated policy be retained in Section 440 and be renumbered to facilitate searching of the database.

In considering policies for consolidation, the Council employed the following approach:

1. Search the current AMA Policy Database (search terms included influenza, flu, vaccine, immunization).
2. Identify outmoded and outdated policies.
3. Group similar policies (or parts of policies) together into one section. To facilitate review and comparison, all pertinent AMA policies or policy elements reflected in the consolidation are cited in their entirety.
4. Edit the language of each proposed policy so that it is coherent and easily understood, without altering its meaning or intent.
5. Recommend that the House adopt the consolidated policies on influenza vaccine availability and distribution, healthcare worker and patient influenza immunization, adult immunization, reimbursement for influenza vaccine, and pandemic preparedness for influenza in their entirety and that the House rescind current AMA policies that are duplicative or outmoded.

To that end, the following policies are recommended to be directly rescinded because they already have been implemented, are obsolete, or are superseded by other policies

- H-440.896 Influenza Vaccine Availability and Distribution
- D-440.990 Influenza Vaccine Delays and the 2001-2002 Influenza Season: Update
- D-440.993 Influenza Vaccine Availability And Distribution
- D-440.962 Avian Influenza Preparedness for Guam and Other Border States and Territories
- D-440.941 Preventing Spread of Novel H1N1 Flu Virus and Spreading the Word

Two appendices are attached to this report to facilitate comparison and tracking of proposed policy changes.

- Appendix A presents the Council's recommended language for consolidated House policies and policies which comprise the consolidation.
- Appendix B presents 5 current policies that the Council believes should be rescinded.

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 the consolidated policy listed in Appendix A be added to the AMA Policy Database.

2. That the following policies be rescinded because they are outdated or duplicative of policies presented in Appendix A:

   H-440.896 Influenza Vaccine Availability and Distribution
   D-440.941 Preventing Spread of Novel H1N1 Flu Virus and Spreading the Word
   D-440.962 Avian Influenza Preparedness for Guam and Other Border States and Territories
   D-440.990 Influenza Vaccine Delays and the 2001-2002 Influenza Season: Update
   D-440.993 Influenza Vaccine Availability and Distribution

APPENDIX A - Proposed Consolidation of House Policy on Influenza and Influenza Vaccine

H-440.XXX Influenza Vaccine Availability and Distribution
Our AMA will: (1) continue efforts to communicate strongly to its partners involved in influenza vaccine production and distribution that physicians must receive influenza vaccines in a timely and equitable manner in order to help immunize all patients ≥6 months of age as recommended by the Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP); (2) urge manufacturers and distributors of influenza vaccine to provide a dedicated ordering system for small- and medium-size medical practices to pre-order vaccine up to an appropriate volume threshold; (3) support federal actions to allow physicians (MDs and DOs) to form purchasing alliances to allow for competitive purchasing of influenza vaccine comparable to large purchasers currently supplying pharmacy and grocery chain stores with influenza vaccine; (4) communicate current ACIP recommendations on the influenza vaccine to physicians and assist the CDC in disseminating its informational letters and bulletins to physicians and other providers of the influenza vaccine when they become available in order to ensure compliance with the ACIP recommendations with respect to immunization of patients with influenza vaccine; (5) work with the CDC and other immunization partners to explore options to provide for timely influenza immunization of indigent or underserved populations, including exploring options to provide for the timely redistribution of state and federally funded influenza vaccines to facilities or groups within the state willing to appropriately manage, distribute, and administer the vaccine to indigent or underserved populations; (6) continue its collaboration with the CDC and other stakeholders in influenza vaccination to work to achieve the influenza immunization goals of Healthy People 2020, with particular attention to improving demand for vaccine and achieving stability in the vaccine supply; (7) work with local public health officers through the Federation to respond to community flu vaccine shortages and possible influenza outbreaks to protect the public health; and, (8) urge the federal government to support, as a national priority, the development of safe and effective influenza vaccines employing new technologies and to continue to support adequate distribution to ensure that there will be an affordable, available and safe supply of influenza vaccine on an annual basis. (H-440.873(5); H-973(5); D-440.942; D-440.964; D-440.973; D-440.974(2); D-440.992(2,4)

H-440.XXX Recommendations for Healthcare Worker and Patient Influenza Immunization
Our AMA (1) reaffirms its support for universal influenza vaccination of health care workers (HCWs) and supports universal immunization of HCWs against seasonal and pandemic influenza through vaccination programs undertaken by health care institutions in conjunction with medical staff leadership; (2) encourages all hospitals, health care systems, and health care providers to immunize providers and appropriate patients as defined by the Advisory Committee on Immunization Practices guidelines against both influenza and pertussis, as a priority, both for their own protection and to reduce the risk of transmission to others; (3) will work to ensure that hospitals and skilled nursing facilities have a system for measuring and maximizing the rate of influenza immunization for health care workers. (H-440.878; D-440.967)

H-440.XXX Adult Immunization
Our AMA (1) supports the development of a strong adult and adolescent immunization program in the United States; (2) encourages physicians and other health and medical workers (in practice and in training) to set positive examples by assuring that they are completely immunized; (3) urges physicians to advocate immunization with all adult patients to whom they provide care, to provide indicated vaccines to ambulatory as well as hospitalized patients, and to maintain complete immunization records, providing copies to patients as necessary; (4) encourages the National Influenza Vaccine Summit to examine mechanisms to ensure that patient immunizations get communicated to their personal physician; (5) promotes use of available public and professional educational materials to increase use of vaccines and toxoids by physicians and to increase requests for and acceptance of these antigens by adults for whom they are indicated; and (6) encourages third party payers to provide coverage for adult immunizations. (H-440.973; H-440.883; H-440.896)

H-440.XXX Reimbursement for Influenza Vaccine
Our AMA: (1) will work with third party payers, including the Centers for Medicare and Medicaid Services, to establish a fair reimbursement price for the flu vaccine; (2) encourage the manufacturers of influenza vaccine to publish the purchase price by June 1st each year; (3) shall seek federal legislation or regulatory relief, or otherwise work with the federal government to increase Medicare reimbursement levels for flu vaccination and other vaccinations. (D-440.983; D-440.989)

H-440.XXX Pandemic Preparedness for Influenza
In order to prepare for a potential influenza pandemic, our AMA: (1) urges the Department of Health and Human Services Emergency Care Coordination Center, in collaboration with the leadership of the Centers for Disease Control and Prevention (CDC), state and local health departments, and the national organizations representing them, to urgently assess the shortfall in funding, staffing, vaccine, drug, and data management capacity to prepare for and respond to an influenza pandemic or other serious public health emergency; (2) urges Congress and the Administration to work to ensure adequate funding and other resources: (a) for the CDC, the National Institutes of Health (NIH) and other appropriate federal agencies, to support implementation of an expanded capacity to produce the necessary vaccines and anti-viral drugs and to continue development of the nation's capacity to rapidly vaccinate the entire population and care for large numbers of seriously ill people; and (b) to bolster the infrastructure and capacity of state and local health department to effectively prepare for, respond to, and protect the population from illness and death in an influenza pandemic or other serious public health emergency; (3) urges the CDC to develop and disseminate electronic instructional resources on procedures to follow in an influenza epidemic, pandemic, or other serious public health emergency, which are tailored to the needs of physicians and medical office staff in ambulatory care

settings; (4) supports the position that: (a) relevant national and state agencies (such as the CDC, NIH, and the state departments of health) take immediate action to assure that physicians, nurses, other health care professionals, and first responders having direct patient contact, receive any appropriate vaccination in a timely and efficient manner, in order to reassure them that they will have first priority in the event of such a pandemic; and (b) such agencies should publicize now, in advance of any such pandemic, what the plan will be to provide immunization to health care providers; (6) will monitor progress in developing a contingency plan that addresses future influenza vaccine production or distribution problems and in developing a plan to respond to an influenza pandemic in the United States. (D-440.945; D-440.946; D-440.965(1b,2); D-440.992(3))

Reflects* current policies:

H-440.873 Update on Influenza Immunization
Our AMA will continue efforts to communicate strongly to its partners involved in influenza vaccine production and distribution that physicians who serve high-risk populations must receive influenza vaccines in a timely and equitable manner in order to serve these populations as recommended by the CDC's Advisory Committee on Immunization Practices and will broadly disseminate Board of Trustees Report 26-A-07, Update on Influenza Immunization, to specialty and state medical societies. (BOT Rep. 26, A-07)

H-440.878 Pertussis and Influenza Immunization
Our AMA encourages all hospitals, health care systems, and health care providers to immunize providers and appropriate patients as defined by the Advisory Committee on Immunization Practices guidelines against both influenza and pertussis, as a priority, both for their own protection and to reduce the risk of transmission to others. (Res. 510, A-06; Reaffirmed in lieu of Res. 813, I-06)

H-440.883 United States Influenza Vaccine Supply: Update and Future Directions for Adult Immunization
Our American Medical Association supports the development of a strong adult and adolescent immunization program in the United States. (BOT Rep. 28, I-04; Reaffirmation A-05)

H-440.973 Immunization of Adults
Our AMA (1) encourages physicians and other health and medical workers (in practice and in training) to set positive examples by assuring that they are completely immunized; (2) urges physicians to advocate immunization with all adult patients to whom they provide care, to provide indicated vaccines to ambulatory as well as hospitalized patients, and to maintain complete immunization records, providing copies to patients as necessary; (3) promotes use of available public and professional educational materials to increase use of vaccines and toxoids by physicians and to increase requests for and acceptance of these antigens by adults for whom they are indicated; (4) encourages third party payers to provide coverage for adult immunizations; and (5) will urge manufacturers and distributors of influenza vaccine to provide a dedicated ordering system for small- and medium-size medical practices to pre-order vaccine up to an appropriate volume threshold. (Res. 3, I-86; Reaffirmed: Sunset Report, I-96; Reaffirmed: CSAPH Rep. 3, A-06; Appended: Sub. Res. 514, A-06; Reaffirmation A-08)

D-440.942 Influenza Vaccine Distribution
Our American Medical Association will work with the Centers for Disease Control and Prevention and other immunization partners to explore options to provide for timely influenza immunization of indigent or underserved populations, including exploring options to provide for the timely redistribution of state and federally funded influenza vaccines to facilities or groups within the state willing to appropriately manage, distribute, and administer the vaccine to indigent or underserved populations. (BOT Action in response to referred for decision Res. 505, A-09)

D-440.945 Instructional Resources on Epidemic and Pandemic Flu for Medical Office Staffs
Our AMA urges the Centers for Disease Control and Prevention to develop and disseminate electronic instructional resources on procedures to follow in an influenza epidemic, pandemic, or other serious public health emergency, which are tailored to the needs of physicians and medical office staff in ambulatory care settings. (Sub. Res. 424, A-09)

D-440.946 Strengthen State and Local Health Department Pandemic Response Capacity
1. Our AMA urges the Department of Health and Human Services Emergency Care Coordination Center, located within the office of the Assistant Secretary for Preparedness and Response, in collaboration with the leadership of the Centers for Disease Control and Prevention, state and local health departments, and the national organizations representing them, to urgently assess the shortfall in funding, staffing, vaccine, drug, and data management capacity to prepare for and respond to an influenza pandemic or other serious public health emergency. 2. Our AMA urges the President and the Congress to take rapid action to provide the necessary funding and other resources to bolster the infrastructure and capacity of state and local health departments to effectively prepare for, respond to, and protect the population from illness and death in an influenza pandemic or other serious public health emergency. (Sub. Res. 421, A-09)

* When portions of a policy are underlined, only this part of the policy is captured by the consolidation. Other parts are deemed obsolete or have already been implemented.

D-440.964 Flu Vaccine Supply
Our AMA will urge the federal government to support, as a national priority, the development of safe and effective influenza vaccines employing new technologies and to continue to support adequate distribution to ensure that there will be an affordable, available and safe supply of influenza vaccine on an annual basis. (Res. 517, A-05)

D-440.965 Avian and Other Influenza Pandemic
(1) Our AMA will: (a) strive to increase the number of people vaccinated annually against influenza, particularly high risk patients, by working with appropriate stakeholders to expand understanding among physicians and patients about who is included in the "high risk" population; and (b) in order to prepare for a potential influenza pandemic, lobby Congress and the Administration to ensure that appropriate funding is provided to the Centers for Disease Control and Prevention, the National Institutes of Health, and other appropriate federal agencies, to support implementation of an expanded capacity to produce the necessary vaccines and anti-viral drugs and to continue development of the nation's capacity to rapidly vaccinate the entire population and care for large numbers of seriously ill people. (2) AMA policy is that health care professionals and first responders will be the first line of defense in combating the effects of an influenza pandemic, that the involved national and state agencies (such as the Centers for Disease Control and Prevention, National Institutes of Health and the state departments of health) take immediate action to assure that physicians, nurses, other health care professionals, and first responders having direct patient contact, receive any appropriate vaccination in a timely and efficient manner, in order to reassure them that they will have first priority in the event of such a pandemic; and our AMA will encourage that these agencies publicize now, in advance of any such pandemic, what the plan will be to provide immunization to health care providers. (Res. 514, A-05; Appended: Res. 530, A-06)

D-440.967 Influenza Immunization for Health Care Workers
1. Our AMA will work to ensure that hospitals and skilled nursing facilities have a system for measuring and maximizing the rate of influenza immunization for health care workers. 2. Our AMA: (a) reaffirms its support for universal influenza vaccination of health care workers (HCWs); and (b) supports universal immunization of HCWs against seasonal and pandemic influenza through vaccination programs undertaken by health care institutions in conjunction with medical staff leadership. (Res. 518, A-05; Reaffirmed in lieu of Res. 813, I-06; Appended: Res. 7, I-10)

D-440.973 Influenza Vaccine Orders from Physicians (MDs and DOs)
Our AMA will immediately take action through the federal government to allow physicians (MDs and DOs) to form purchasing alliances to allow for competitive purchasing of influenza vaccine comparable to large purchasers currently supplying pharmacy and grocery chain stores with influenza vaccine. (Res. 714, I-04; Reaffirmation A-05)

D-440.974 United States Influenza Vaccine Supply: Update and Future Directions for Adult Immunization
Our AMA will (1) work with its partners in immunization and other appropriate stakeholders, such as those in the National Influenza Vaccine Summit, to develop recommendations on the best methods for achieving a strong adult and adolescent immunization program in the United States; and (2) continue its collaboration with the Centers for Disease Control and Prevention and other stakeholders in influenza vaccination to work to achieve the influenza immunization goals of Healthy People 2010, with particular attention to improving demand for vaccine and achieving stability in the vaccine supply. (BOT Rep. 28, I-04; Reaffirmation A-05)

D-440.983 Cost-Effective Flu Vaccine/Medicare Reimbursement Level
Our AMA shall seek federal legislation or regulatory relief, or otherwise work with the federal government to increase Medicare reimbursement levels for flu vaccination and other vaccinations. (Res. 503, A-02; Reaffirmation A-05)

D-440.989 Influenza Vaccine
Our AMA will: (1) work with third party payers, including the Centers for Medicare and Medicaid Services, to establish a fair reimbursement price for the flu vaccine; and (2) encourage the manufacturers of influenza vaccine to publish the purchase price by June 1st each year. (Res. 414, I-01)

D-440.992 Production and Distribution of the Influenza Vaccine: Delays and Shortages
Our AMA: (1) will continue to work with the Centers for Disease Control and Prevention (CDC) to organize, when possible, a second Roundtable meeting of influenza vaccine stakeholders, to assess the current influenza vaccine season and to develop a contingency plan to be implemented in the event of another problem in vaccine production or distribution; (2) will communicate current ACIP recommendations on the influenza vaccine to physicians and assist the CDC in disseminating its informational letters and bulletins to physicians and other providers of the influenza vaccine when they become available; (3) will monitor progress in developing a contingency plan that addresses future influenza vaccine production or distribution problems and in developing a plan to respond to an influenza pandemic in the United States; (4) will support mechanisms to increase influenza vaccine supply and vaccine demand among physicians, other providers, and consumers to ensure the goals of Healthy People 2010 are achieved; and (5) Board of Trustees will immediately investigate issues, including cost, reimbursement, availability, and distribution, which may adversely affect the ability of physicians to provide influenza vaccine to their patients in the upcoming (2001-2002) influenza season. (BOT Rep. 36, A-01; Reaffirmation I-04; Reaffirmation A-05)

APPENDIX B - Current AMA Policies Recommended for Deletion

H-440.896 Influenza Vaccine Availability and Distribution
Our AMA: (1) will work with all appropriate agencies and organizations, including vaccine manufacturers, to prioritize the distribution channels for influenza vaccine to assure the vaccine is available to patients in accordance with Centers for Disease Control and Prevention guidelines for high risk patients; (2) urges Congress and the Secretary of the US Department of Health and Human Services to develop a mechanism to assure appropriate distribution of influenza vaccine initially to those providers, public and private, who will immunize the highest risk individuals first, and then use the remainder to protect other members of the public; (3) will work with the Centers for Disease Control and Prevention, appropriate medical specialty societies, and influenza immunization partners to ensure, in future influenza seasons, adequate influenza vaccine distribution and administration to the high-priority populations as recommended by the Advisory Committee on Immunization Practices (ACIP); (4) will work with the CDC, through the National Influenza Vaccine Summit, to ensure compliance with the ACIP's annual recommendations with respect to the immunization of patients prioritized to receive influenza vaccine; and (5) advocates vigorously that for every influenza season, an adequate number of doses of every manufacturer's vaccine supply be sold directly to health care providers immunizing patients identified by the ACIP as being high priority for receiving influenza vaccine; (6) will prepare a comprehensive report educating physicians on the complexities of influenza vaccine supply and distribution; and (7) encourages the National Influenza Vaccine Summit to re-examine: (a) the issue of equitable distribution of influenza vaccine, especially during periods of vaccine shortage, and (b) mechanisms to ensure that patient immunizations get communicated to their personal physician. (Sub. Res. 416, I-00; Reaffirmation A-05; Appended: Sub. Res. 514, A-06; Reaffirmation A-10; Reaffirmed and Appended: Sub. Res. 914, I-10; Reaffirmed in lieu of Res. 422, A-11: BOT action in response to referred for decision Res. 422, A-11).

D-440.941 Preventing Spread of Novel H1N1 Flu Virus and Spreading the Word
Our American Medical Association will create and cause wide dissemination of a press release asking the entertainment, food and travel industry, spectator sports venues, places of worship and other such places where very large groups of people come together, to develop their own H1N1 Flu Disaster Plans consistent with the Centers for Disease Control and Prevention and respective state health department recommendations. (Res. 921, I-09)

D-440.962 Avian Influenza Preparedness for Guam and Other Border States and Territories
Our AMA will (1) lobby the Administration to ensure that the Centers for Disease Control and Prevention (CDC), other federal agencies and the World Health Organization (WHO) assist Guam with the necessary testing kits and other tools necessary for Guam to detect and contain Avian Influenza; and (2) assist other areas of the US to be considered as "border states or territories" for surveillance of this Avian Influenza from Asia, so that the CDC, other federal agencies and WHO may prioritize their resources to detect and contain this virus. (Res. 722, I-05)

D-440.990 Influenza Vaccine Delays and the 2001-2002 Influenza Season: Update
(1) Our AMA will continue to work with the Centers for Disease Control and Prevention, other federal agencies, and other stakeholders involved in the production, distribution, and administration of influenza vaccine to: (a) resolve the specific problems (i.e., distributors engaging in price inflation, mass vaccinators who do not comply with Advisory Committee on Immunization Practices [ACIP] recommendations, and inadequate Medicare/Medicaid reimbursement) identified in the implementation of the current plan to address influenza vaccine delays in 2001-2002; and (b) address the long-term goal of adequate vaccine supplies to meet Healthy People 2010 goals which will include increasing the industrial base for vaccine production and expanding the current limited protection from liability for both manufacturers and those that administer vaccines. (2) Our AMA Board of Trustees will report back to the House of Delegates at the 2002 Annual Meeting regarding the current status of our AMA's activities to address issues of price instability, vaccine availability, and liability related to the flu vaccine. (BOT Rep. 28, I-01; Reaffirmation I-04; Reaffirmation A-05)

D-440.993 Influenza Vaccine Availability And Distribution
Our AMA: (1) will demand a Congressional investigation of the maldistribution and unjustified price increases associated with the year 2000 flu vaccine; (2) will urge physicians and their patients to write their Congressional representatives in support of an investigation of the 2000 experience with influenza vaccine distribution and pricing; (3) will explore options for the appropriate oversight of the supply, distribution and marketing of flu vaccines by appropriate agencies within the US Department of Health and Human Services; (4) and the Federation will work with local public health officers through state and county medical societies to respond to community flu vaccine shortages and possible influenza outbreaks to protect the public health; and (5) will report back to the House of Delegates on efforts to ensure appropriate distribution of influenza vaccines at the 2001 Annual Meeting. (Sub. Res. 416, I-00; Reaffirmation I-04)