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ORIGINAL RESEARCH

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Dr Farzad Mostashari Answers Why Data Is 'Oxygen' for Innovation
http://bit.ly/1f6SSe2

Farzad Mostashari, MD, ScM, *visiting fellow, Brookings Institution, former national coordinator for health information technology, US Department of Health and Human Services, discusses how data and digitization are driving innovation in healthcare.*

J0401

Effective 1/1/14 for
Abilify Maintena® (aripiprazole) for
Extended-Release Injectable Suspension

INDICATION and IMPORTANT SAFETY INFORMATION for Abilify Maintena® (aripiprazole) for extended-release injectable suspension

INDICATION

Abilify Maintena is an atypical antipsychotic indicated for the treatment of schizophrenia.

- **Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials.**

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Abilify Maintena is not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with oral aripiprazole.

FOR THE **TREATMENT OF SCHIZOPHRENIA**

An option that may help your members delay relapse

Abilify Maintena® (aripiprazole) significantly delayed the time to relapse* vs placebo (*P*<0.0001)

Visit AbilifyMaintena.com for product information and Formkit.com for formulary information.

*In a Phase III, 52-week, double-blind, randomized-withdrawal clinical trial; Abilify Maintena (n=269) vs placebo (n=134).

IMPORTANT SAFETY INFORMATION *(continued)*

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including Abilify Maintena. Rare cases of NMS occurred during aripiprazole treatment. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. There is no known treatment for established TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Continued on next page.

Please see IMPORTANT SAFETY INFORMATION continued, and BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the following pages.

400MG

Abilify Maintena®

(aripiprazole) for extended release injectable suspension

IMPORTANT SAFETY INFORMATION for Abilify Maintena® (aripiprazole) for extended-release injectable suspension *(continued)*

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting low-density lipoproteins (LDLs), and fasting/nonfasting high-density lipoproteins (HDLs).
- **Weight Gain:** Weight gain has been observed. Clinical monitoring of weight is recommended.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension. Abilify Maintena should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported. Patients with a history of clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy while receiving Abilify Maintena. In such patients, consider discontinuation of Abilify Maintena at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

Seizures/Convulsions: Abilify Maintena should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: Abilify Maintena may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery including automobiles until they are certain Abilify Maintena does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with Abilify Maintena; use caution in patients at risk for aspiration pneumonia.

Alcohol: Advise patients to avoid alcohol while taking Abilify Maintena.

Concomitant Medication: Dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the Abilify Maintena dosage may need to be increased. Avoid the concomitant use of CYP3A4 inducers with Abilify Maintena for greater than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels. Dosage adjustments are not recommended for patients with concomitant use of CYP3A4 inhibitors, CYP2D6 inhibitors or CYP3A4 inducers for less than 14 days.

Most commonly observed adverse reaction: The safety profile of Abilify Maintena is expected to be similar to that of oral aripiprazole. In patients who tolerated and responded to oral aripiprazole and single-blind Abilify Maintena and were then randomized to receive Abilify Maintena or placebo injections, the incidence of adverse reactions was similar between the two treatment groups. The adverse reaction ≥ 5% incidence and at least twice the rate of placebo for oral aripiprazole vs placebo, respectively, was:

- Akathisia (8% vs 4%) in adult patients with schizophrenia.

Injection Site Reactions: In the open-label, stabilization phase of a study with Abilify Maintena in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for Abilify Maintena-treated patients.

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy/Nursing: Based on animal data, may cause fetal harm. Abilify Maintena should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on adjacent pages.

ABILIFY MAINTENA™ (aripiprazole) for extended-release injectable suspension, for intramuscular use

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details, please see *Full Prescribing Information and Medication Guide*.)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death
- ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis

INDICATIONS AND USAGE: ABILIFY MAINTENA (aripiprazole) is indicated for the treatment of schizophrenia. Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials.

CONTRAINDICATIONS: ABILIFY MAINTENA is contraindicated in patients with a known hypersensitivity to aripiprazole. Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis have been reported in patients receiving aripiprazole.

WARNINGS AND PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, in oral aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse reactions in patients treated with oral aripiprazole. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including ABILIFY MAINTENA. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY MAINTENA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with ABILIFY MAINTENA drug discontinuation should be considered. However, some patients may require treatment with ABILIFY MAINTENA despite the presence of the syndrome.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. Although the following metabolic data were collected in patients treated with oral formulations of aripiprazole, the findings pertain to patients receiving ABILIFY MAINTENA as well.

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with diabetic ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with aripiprazole. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes), who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the atypical antipsychotic drug.

  In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in aripiprazole-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 1 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 1: Changes in Fasting Glucose From Placebo-controlled Monotherapy Trials in Adult Patients

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Aripiprazole	31/822	3.8
		Placebo	22/605	3.6
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Aripiprazole	31/176	17.6
		Placebo	13/142	9.2

At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

  There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

  Table 2 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 2: Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	Aripiprazole	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	Aripiprazole	40/539	7.4
	Placebo	30/431	7.0
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	Aripiprazole	2/332	0.6
	Placebo	2/268	0.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	Aripiprazole	121/1066	11.4
	Placebo	99/794	12.5

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/ nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in aripiprazole-treated patients was +0.3 kg (N=1673) compared to –0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

  Table 3 shows the percentage of adult patients with weight gain ≥7% of body weight in the 13 pooled placebo-controlled monotherapy trials.

Table 3: Percentage of Patients From Placebo-controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	n (%)
Weight gain ≥7% of body weight	Schizophrenia[a]	Aripiprazole	852	69 (8.1)
		Placebo	379	12 (3.2)
	Bipolar Mania[b]	Aripiprazole	719	16 (2.2)
		Placebo	598	16 (2.7)

[a]4-6 weeks' duration. [b]3 weeks' duration.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. Orthostasis occurred in 4/576 (0.7%) patients treated with ABILIFY MAINTENA during the stabilization phase, including abnormal orthostatic blood pressure (1/576, 0.2%), postural dizziness (1/576, 0.2%), presyncope (1/576, 0.2%) and orthostatic hypotension (1/576, 0.2%).

In the stabilization phase, the incidence of significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) was 0.2% (1/575).

Leukopenia, Neutropenia, and Agranulocytosis: *Class Effect:* In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including oral aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC counts until recovery.

Seizures: As with other antipsychotic drugs, use ABILIFY MAINTENA cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment: ABILIFY MAINTENA, like other antipsychotics, may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY MAINTENA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY MAINTENA for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY MAINTENA. ABILIFY MAINTENA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS: The following adverse reactions are discussed in more detail in other sections of the labeling in the *Full Prescribing Information:*

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic Changes *[see Warnings and Precautions (5.5)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Seizures *[see Warnings and Precautions (5.8)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.9)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.10)]*
- Dysphagia *[see Warnings and Precautions (5.11)]*

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety Database of ABILIFY MAINTENA and Oral Aripiprazole: Aripiprazole has been evaluated for safety in 16,114 adult patients who participated in multiple-dose, clinical trials in schizophrenia and other indications, and who had approximately 8,578 patient-years of exposure to oral aripiprazole. A total of 3,901 patients were treated with oral aripiprazole for at least 180 days, 2,259 patients were treated with oral aripiprazole for at least 360 days, and 933 patients continuing aripiprazole treatment for at least 720 days.

ABILIFY MAINTENA 300-400 mg every 4 weeks has been evaluated for safety in 1,287 adult patients in clinical trials in schizophrenia, with approximately 1,281 patient-years of exposure to ABILIFY MAINTENA. A total of 832 patients were treated with ABILIFY MAINTENA for at least 180 days (at least 7 consecutive injections) and 630 patients treated with ABILIFY MAINTENA had at least 1 year of exposure (at least 13 consecutive injections).

The conditions and duration of treatment with ABILIFY MAINTENA included double-blind and open-label studies. The safety profile of ABILIFY MAINTENA is expected to be similar to that of oral aripiprazole. Therefore, most of the safety data presented below are derived from trials with the oral formulation. In patients who tolerated and responded to treatment with oral aripiprazole and single-blind ABILIFY MAINTENA and were then randomized to receive ABILIFY MAINTENA or placebo injections under double-blind conditions, the incidence of adverse reactions was similar between the two treatment groups.

Adverse Reactions of ABILIFY MAINTENA and Oral Aripiprazole: *Adverse Reactions Associated with Discontinuation of Oral Aripiprazole:* Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the incidence of discontinuation due to adverse reactions was 7% in oral aripiprazole-treated and 9% in placebo-treated patients. The types of adverse reactions that led to discontinuation were similar for the aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions of Oral Aripiprazole: Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the only commonly observed adverse reaction associated with the use of oral aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%; placebo 4%).

Less Common Adverse Reactions in Adults Treated with Oral Aripiprazole: Table 4 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with oral aripiprazole (doses ≥2 mg/ day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 4: Adverse Reactions in Short-term, Placebo-controlled Trials in Adult Patients Treated with Oral Aripiprazole

	Percentage of Patients Reporting Reaction[a]	
System Organ Class Preferred Term	**Oral Aripiprazole (n=1843)**	**Placebo (n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a]Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

Dose-Related Adverse Reactions of Oral Aripiprazole: Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed oral doses of aripiprazole (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 mg/day) to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

Injection Site Reactions of ABILIFY MAINTENA: In the open-label, stabilization phase of a study with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for ABILIFY MAINTENA-treated patients. The mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably painful) was minimal and improved in subjects receiving ABILIFY MAINTENA from the first to the last injection in the open-label, stabilization phase (6.1 to 4.9).

Investigator evaluation of the injection site for pain, swelling, redness and induration following injections of ABILIFY MAINTENA in the open-label, stabilization phase were rated as absent for 74%-96% of subjects following the first injection and 77%-96% of subjects following the last injection.

Extrapyramidal Symptoms of Oral Aripiprazole: In short-term, placebo-controlled trials in schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia, for oral aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, –0.05).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesias) did not show a difference between aripiprazole and placebo.

Dystonia: Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials of Oral Aripiprazole: The adverse reactions reported in a 26-week, double-blind trial comparing oral aripiprazole and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for oral aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of oral aripiprazole. In addition, in a long-term, active-controlled study, the incidence of tremor was 5% (40/859) for oral aripiprazole.

Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Aripiprazole: Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in other parts of *Adverse Reactions (6),* or those considered in *Warnings and Precautions (5)* or *Overdosage (10)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders: ≥1/1000 patients and <1/100 patients - thrombocytopenia; Cardiac Disorders: ≥1/1000 patients and <1/100 patients - palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, angina pectoris, myocardial ischemia; <1/1000 patients - atrial flutter, supraventricular tachycardia, ventricular tachycardia; *Eye Disorders:* ≥1/1000 patients and <1/100 patients - photophobia, diplopia, eyelid edema, photopsia; *Gastrointestinal Disorders:* ≥1/1000 patients and <1/100 patients - gastroesophageal reflux disease, swollen tongue, esophagitis; <1/1000 patients - pancreatitis; *General Disorders and Administration Site Conditions:* ≥1/100 patients - asthenia, peripheral edema, chest pain; ≥1/1000 patients and <1/100 patients - face edema, angioedema; <1/1000 patients - hypothermia; *Hepatobiliary Disorders:* <1/1000 patients - hepatitis, jaundice; *Immune System Disorders:* ≥1/1000 patients and <1/100 patients - hypersensitivity; *Injury, Poisoning, and Procedural Complications:* ≥1/100 patients - fall; <1/1000 patients - heat stroke; Investigations: ≥1/1000 patients and <1/100 patients - blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased; <1/1000 patients - blood lactate dehydrogenase increased, glycosylated hemoglobin increased; *Metabolism and Nutrition Disorders:* ≥1/1000 patients and <1/100 patients - anorexia, hyponatremia, hypoglycemia, polydipsia; <1/1000 patients - diabetic ketoacidosis; *Musculoskeletal and Connective Tissue Disorders:* ≥1/1000 patients and <1/100 patients - muscle rigidity, muscular weakness, muscle tightness, mobility decreased; <1/1000 patients - rhabdomyolysis; *Nervous System Disorders:* ≥1/100 patients - coordination abnormal; ≥1/1000 patients and <1/100 patients - speech disorder, hypokinesia, hypotonia, myoclonus, akinesia, bradykinesia; <1/1000 patients - choreoathetosis; *Psychiatric Disorders:* ≥1/100 patients - suicidal ideation; ≥1/1000 patients and <1/100 patients - loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation; <1/1000 patients - catatonia, sleepwalking; *Renal and Urinary Disorders:* ≥1/1000 patients and <1/100 patients - urinary retention, polyuria, nocturia; *Reproductive System and Breast Disorders:* ≥1/1000 patients and <1/100 patients - menstruation irregular, erectile dysfunction, amenorrhea, breast pain; <1/1000 patients - gynecomastia, priapism; *Respiratory, Thoracic, and Mediastinal Disorders:* ≥1/100 patients - nasal congestion, dyspnea; *Skin and Subcutaneous Tissue Disorders:* ≥1/100 patients - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; ≥1/1000 patients and <1/100 patients - pruritus, photosensitivity reaction, alopecia, urticaria.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of oral aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm).

DRUG INTERACTIONS: Carbamazepine or Other CYP3A4 Inducers: Concomitant use of ABILIFY MAINTENA with carbamazepine or other CYP3A4 inducers decreases the concentrations of aripiprazole. Avoid use of ABILIFY MAINTENA in combination with carbamazepine and other inducers of CYP3A4 for greater than 14 days *[see Indications and Usage, Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].*

Ketoconazole or Other Strong CYP3A4 Inhibitors: Concomitant use of ABILIFY MAINTENA with ketoconazole or other CYP3A4 inhibitors for more than 14 days increases the concentrations of aripiprazole and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].* Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of ketoconazole or other inhibitors of CYP3A4 with ABILIFY MAINTENA does not require a dose adjustment.

Quinidine or Other Strong CYP2D6 Inhibitors: Concomitant use of ABILIFY MAINTENA with quinidine or other CYP2D6 inhibitors increases the concentrations of aripiprazole after longer-term use (i.e., over 14 days) and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].* Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of quinidine or other CYP2D6 inhibitors with ABILIFY MAINTENA does not require a dose adjustment.

CNS Depressants: Given the CNS depressant effects of aripiprazole, use caution when ABILIFY MAINTENA is taken in combination with other centrally-acting drugs or alcohol.

Anti-Hypertensive Agents: Due to its α_1-adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category C: Risk Summary:* Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs (including ABILIFY MAINTENA) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits at doses 1-10 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on a mg/m^2 body surface area. ABILIFY MAINTENA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations: Fetal/Neonatal Adverse Reactions: Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Animal Data: Pregnant rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day on a mg/m^2 body surface area) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats receiving aripiprazole injection intravenously (3 mg/kg/day, 9 mg/kg/day, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

Pregnant rabbits were treated with oral doses of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day (2 times, 3 times, and 11 times human exposure at the oral MRHD of 30 mg/day based on AUC and 6 times, 19 times, and 65 times the oral MRHD of 30 mg/day based on mg/m^2 body surface area) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 mg/ kg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 mg/kg and 100 mg/kg), and minor skeletal variations (100 mg/kg).

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the oral MRHD based on AUC and is 6 times the oral MRHD of 30 mg/day based on mg/m^2 body surface area.

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral MRHD of 30 mg/day on a mg/m^2 body surface area) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

In rats receiving aripiprazole injection intravenously (3 mg/kg/day, 8 mg/kg/day, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 mg/kg and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

Nursing Mothers: Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ABILIFY MAINTENA in patients <18 years of age have not been evaluated.

Geriatric Use: Safety and effectiveness of ABILIFY MAINTENA in patients >60 years of age have not been evaluated. In oral single-dose pharmacokinetic studies (with aripiprazole given in a single oral dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients. Also, the pharmacokinetics of oral aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment of ABILIFY MAINTENA is recommended for elderly patients *[see also Boxed Warning and Warnings and Precautions (5.1)].*

CYP2D6 Poor Metabolizers: Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). Dosage adjustment is recommended in CYP2D6 poor metabolizers due to high aripiprazole concentrations *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].*

OVERDOSAGE: Human Experience: The largest known case of acute ingestion with a known outcome involved 1260 mg of oral aripiprazole (42 times the maximum recommended daily dose) in a patient who fully recovered.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdosage: In case of overdosage, call the Poison Control Center immediately at 1-800-222-1222.

PATIENT COUNSELING INFORMATION: Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ABILIFY MAINTENA.

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 09US12L-1001B February 2013

You have to have some skin in the game. That expression—so common in business—refers to the fact that financial incentives generate action; or to use another well-known phrase, people "follow the money." The components of the healthcare system, from individual doctors to insurance companies to giant hospital systems, are hardly immune to basic economics. The trouble with healthcare as we have known it is that the incentives reward the wrong things. But changing a system that everyone knows to one that few understand is not easy, even if there's agreement that change must come. This issue of *The American Journal of Accountable Care* includes pieces on realigning financial incentives to improve care, both on a small and a large scale. Suzanne F. Delbanco, PhD, writes about various incentive models that could be used to reduce the number of early elective Caesarean sections, long recognized as a risky, unnecessary driver of healthcare costs. It's no surprise that one of the most effective methods was refusing to pay for these procedures. Delbanco reports that when BlueCross BlueShield of South Carolina teamed with the state's Medicaid system to say "No," the initiative reduced unwarranted elective inductions by 50%. On the macro scale, Susan Dentzer, senior policy advisor for the Robert Wood Johnson Foundation, reports on what is known so far about the experiment with the 32 "Pioneer" accountable care organizations, or Pioneer ACOs. Dentzer connects the dots: there was not enough skin in the game for either the ACOs or Medicare. Crafters of the Pioneer program, fearful of political fallout from too much disruption, failed to include enough "carrots or sticks," as she calls them. More of both are needed if larger healthcare systems can really change the way they do business. Healthcare can talk about change, but until it sets up a rewards structure that encourages entrepreneurship and creative thinking, progress will be slow. Regulators should focus on taking out barriers to change, not setting up new ones. The time for caution, of simply dipping toes in the water, has passed. The Affordable Care Act is here, and if it's going to work, rewards for the best care must come now.

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The American Journal of Accountable Care™

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The ongoing transformation of the American healthcare system is notable for the diversity of strategies being explored. If there is any common thread, it may be the desire to create "accountability." *The American Journal of Accountable Care* is dedicated to exploring all avenues toward accountability.

One approach to accountability focuses on payment reform. Medicare's accountable care organization (ACO) program exemplifies this strategy, but other versions exist. For example, Oregon has adopted a program of coordinated care organizations for Medicaid that imposes a global budget strategy.[1] Arkansas has adopted a multipayer bundled payment strategy. Private payers, such as Blue Cross Blue Shield (BCBS) of Massachusetts, have developed global-budget models.[2] Carefirst in the Washington, DC, metro area has implemented a patient-centered medical home model that puts providers at risk. Delbanco describes models for childbirth at WellPoint, a Hoag and Blue Shield of California partnership, and BCBS of South Carolina.[3] These models all differ in scope and detail. Yet, they typically rest on 3 fundamental pillars: transferring risk (sometimes upside only) to providers, incorporating performance bonuses related to quality measures, and data support.

Another approach focuses on changing beneficiary incentives to encourage patients to be accountable for their care. Such strategies are exemplified by high-deductible plans, tiered networks, reference pricing plans, and value-based insurance design (V-BID) plans. New tools to help beneficiaries make choices by increasing the pricing transparency, such as that offered by Castlight, are just coming to market. Avik Roy, in this issue, discusses benefit design innovation in Medicaid and calls for more experimentation.[4]

The speed of innovation exceeds our knowledge about what works; evaluation is complex. Success may depend on the environment surrounding the innovation and may reflect multiple synergistic strategies, as opposed to just a single strategy. Surely, program details and execution matter. Some programs may have growing effects over time. Nevertheless, ongoing evaluation is important, though generally just in nascent stages. For example, we know the Alternative Quality Contract, launched by BCBS of Massachusetts, reduced spending and improved outcomes.[2] Promising evidence regarding reference pricing is also emerging.[5] Yet, as Susan Dentzer notes in this issue, evaluation of Medicare's flagship Pioneer ACO program has not been overwhelmingly positive.[6] It is unclear if that reflects design flaws, implementation issues, or simply the fact that conclusions are being drawn too early in the process. New models will surely emerge, and as Bhandari et al note in this issue, new partnerships may encourage novel innovations.[7]

One way or another, healthcare spending growth will slow, and if the proponents of the many models being implemented are proved right, quality will improve in the process. But success is far from guaranteed. We likely find ourselves in a period of turbulence, as old business models rendered obsolete and new models are emerge. Information is essential to managing in this new world. Our hope is that *The American Journal of Accountable Care* will help all stakeholders find success.

"One way or another, healthcare spending growth will slow, and if the proponents of the many models being implemented are proved right, quality will improve in the process."

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The Arkansas Medicaid "Private Option":

Lots of Hype, but Little Reform

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Over the past year, much has been made of the so-called Medicaid "private option" that Arkansas is implementing under the Affordable Care Act (ACA). Supporters of the private option argue that it will offer Medicaid recipients high-quality private-sector coverage at an equal or lesser cost compared with the traditional Medicaid program. Unfortunately, Medicaid's structural and legal constraints make this outcome highly unlikely. Indeed, it is more probable that Arkansas' private option waiver is left to expire on December 31, 2016, forcing the state to revert to a more traditional Medicaid program.

Background

The ACA, as originally enacted into law, required that states expand their Medicaid programs to all adults with incomes below 138% of the federal poverty level. Those that refused to do so would cease to receive federal support for their pre-ACA Medicaid programs.

Official representatives of 26 states joined a lawsuit, *National Freedom of Independent Business v Sebelius*, challenging the constitutionality of this provision of the health law. The US Supreme Court ruled 7 to 2 that requiring states to expand Medicaid as a condition of receiving pre-ACA Medicaid funds exceeded Congress' authority under the spending clause of the Constitution.

The high court's majority struck this provision from the law, opining that "The constitutional violation is fully remedied by precluding the Secretary [of Health and Human Services] from withdrawing existing Medicaid funds for failure to comply with the requirements set out in the expansion." In other words, the Medicaid expansion was now optional for the states.

Most states with Republican legislatures have taken the Supreme Court up on its grant of leniency, and have thus far forgone the Medicaid expansion. As of January 28, 2014, 25 states had chosen to not expand their Medicaid programs under the ACA.

Arkansas has been a notable exception: its Republican-controlled legislature, in concert with a Democratic governor, passed a nonstandard Medicaid expansion in which Medicaid enrollees would receive privately sponsored health coverage—known as Qualified Health Plans—of comparable design to those offered on the ACA exchanges, or marketplaces, to those with incomes between 138% and 400% of the federal poverty level.

Flaws With Traditional Medicaid

There is much to be gained, in theory, by offering Medicaid enrollees a different type of coverage than that supplied under the traditional Medicaid program.

Because the federal Medicaid statute strictly limits the degree to which beneficiaries are responsible for the costs of their care, patients have a strong incentive to become insensitive to the cost and efficiency of the care they receive. Other legal constraints and fiscal incentives make it difficult for states to focus Medicaid's resources on the most needed healthcare services.

This inefficiency, in turn, has led to widespread waste, fraud, and abuse in the Medicaid program. Waste, fraud, and abuse have caused Medicaid programs to exceed state budgetary targets, crowding out other fiscal priorities.

States have responded to the fiscal pressures from Medicaid by doing 1 thing in particular: lowering provider reimbursement rates. States have broad authority to lower rates without interference from the Centers for Medicare & Medicaid Services (CMS); in addition, lowering provider rates has proved thus far to be the least politically controversial way to rein in state costs.

Physicians have responded by withdrawing from the Medicaid program. According to a 2008 survey by the Center for Studying Health Care Change, a much greater percentage of general practitioners are more likely to reject all new Medicaid patients than they are to reject either Medicare or privately insured patients (35.4% to 13.6% and 5.2%, respectively).[1] Also, a *New England Journal of Medicine* study found that two-thirds of pediatric specialists would not accept appointments from children with acute medical problems, such as uncontrolled asthma, forearm frac-

ture, or new-onset afebrile seizure, if they were enrolled in Medicaid or the Children's Health Insurance Program (also known as CHIP).[2]

These difficulties with physician access are associated with poor health outcomes for Medicaid enrollees. The clinical literature consistently indicates that patients on Medicaid have health outcomes that are significantly worse than those with private insurance. Baicker et al, in the Oregon Health Insurance Experiment, found that "Medicaid coverage generated no significant improvements in measured physical health outcomes" versus being uninsured.[3]

The Private Option Fails to Address Medicaid's Flaws

Does the Arkansas private option address the design flaws in the Medicaid program? Over the mid-to-long term, the answer is no.

The privately sponsored, exchange-based health plans offered to participants in the Medicaid expansion must conform to the requirements of the 1965 Medicaid statute, also known as Title XIX of the Social Security Act. This means that copays, deductibles, and other conventional cost-sharing features of commercial plans are largely prohibited under the private option. In addition, plans must have "wrap-around" features to cover the benefits required by Medicaid, but not by other ACA-based exchange plans.

Provider reimbursement under exchange plans is likely to be higher than that in the traditional Medicaid program, which means that Medicaid beneficiaries' access to physicians may improve in the near term. However, higher reimbursement rates will almost certainly lead to higher program costs.

Higher costs is a significant problem. The federal government's official Medicaid waiver, licensing the Arkansas private option, requires that state Medicaid spending be fiscally comparable to that under the traditional Medicaid program; otherwise, the federal government will be forced to pay more than it had budgeted for the program. If Arkansas fails to meet this fiscal neutrality end point, CMS is likely to decline to allow the program to continue past December 31, 2016. (CMS has declared that waivers related to the ACA Medicaid expansion must expire before 2017.)

What Would a Reformist Private Option Look Like?

In order to address Medicaid's design flaws in a fiscally neutral fashion, states would need far greater flexibility in designing the Medicaid benefit. For example, states should have wide latitude to apply substantial copays to nonurgent utilization of the emergency department and to usage of brand name pharmaceuticals in instances where comparable generic medicines are available. Covered benefits under the private option, rather than conforming to the 1965 Medicaid statute, would also enjoy state-based flexibility, perhaps mirroring the requirements of exchange-based Qualified Health Plans.

Ideally, the federal government would give states full flexibility, through block grants or other mechanisms, to administer a low-income health program entirely of states' own design. This would likely lead to profound efficiencies in the delivery and utilization of healthcare services.

For example, states could offer catastrophic coverage in combination with "concierge" primary care and subsidized health savings accounts, for approximately the same cost as the traditional Medicaid benefit. However, such significant changes to the Medicaid program would require Congressional modifications to the federal Medicaid statute.

Conclusion

For those who believe that the unreformed Medicaid program is worth expanding, despite its grave flaws in efficiency and efficacy, Arkansas' private option is only of consequence insofar as it expands Medicaid. But for those who are concerned about Medicaid's problems, and hope that Arkansas is establishing a pathway for reform, there is much reason for skepticism.

The private option is, in essence, a dressed-up version of the Medicaid managed care initiatives that many other states have adopted. Furthermore, the private option has placed state taxpayers at risk for higher Medicaid costs; if the private option costs more than its proponents project, it is unlikely to continue in anything resembling its current form.

Other states that are looking to Arkansas as a route forward for Medicaid expansion would be better served by seeking far greater flexibility from the federal government. Indeed, in an ideal world, we would replace the Medicaid program entirely with either block grants or a fiscally neutral version of the ACA exchanges.

The Medicaid program was enacted in 1965; in the 5 decades since, insurers have developed considerable amounts of innovation in the cost-effective delivery of healthcare services. Without critical tools like flexible cost sharing and health savings accounts, Medicaid will never offer high-quality health coverage at an affordable price. Regretfully, this is a lesson that Arkansas taxpayers will quickly learn.

Author Affiliations: Avik Roy is a senior fellow at the Manhattan Institute for Policy Research, and author of *How Medicaid Fails the Poor* (Encounter Books, 2013).

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It's Time to Embolden the Nation's Experiments With ACOs

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"Small collective impact." Those 3 words constituted the thrust of the recently released evaluation of Medicare's 32 Pioneer accountable care organizations (ACOs) in their first year of operation (2011-2012).[1] Overall, the Pioneer ACOs saved an estimated $146.9 million for the Medicare program—a sum equal to about .003% of overall net Medicare spending in 2012.

The fact that lower spending from a group of 32 health organizations barely made a blip in the big picture isn't surprising. What's most surprising, based on the evaluation, is that any savings occurred at all, given the complexity of the transition inherent in moving to lower-cost, higher-value care. In fact, the evaluation of the Pioneer results, performed by L&M Policy Research (Washington, DC), opens a window on how complex the process of changing the healthcare delivery system actually is, considering:

Outpatient and physician spending. About half of the Pioneer ACOs saw lower growth rates in the area of spending than did a comparison group of Medicare beneficiaries not aligned with an ACO. The evaluators suggested that these organizations might have been successful in pulling services back into physicians' offices and out of hospital outpatient departments, where the services were reimbursed at a higher rate. That explanation seems plausible enough, and would jibe with a sense that physician-led, cost-conscious ACOs were keeping a tighter rein on the costs of care.

Inpatient spending. More problematic is the finding that, for nearly all of the Pioneer ACOs, there was no difference in inpatient spending compared with their local fee-for-service markets. This outcome seems counterintuitive, since better management of patients with chronic illness, for example, has been expected to lead to lower hospitalization rates.

Postacute care. Perhaps most surprisingly, spending on skilled nursing facilities and home health agencies grew significantly faster among beneficiaries aligned with the Pioneer ACOs than it did for other beneficiaries in the same local markets. The evaluators hypothesize that the Pioneer ACOs may have tried to "substitute higher acuity or a greater volume of [skilled nursing facility] days or home health episodes for acute stays." But if this indeed was the case, why was inpatient spending still relatively high?

It's hard to come away from reading such an analysis without having a lot of questions, and a profound sense that patterns of care in ACOs are still so much in flux that it is hard to make heads or tails of these early results. We also know that some Pioneers have already abandoned the ACO program and switched to the alternative Medicare Shared Savings model. And according to the L&M evaluation, 1 Pioneer ACO actually had *higher* Medicare spending growth than the rest of its overall market.

Beyond concerns about grasping at straws by reading these early evaluations too closely, I worry that there is an even greater risk. Ambiguous results such as these could undermine the case for experimentation, and deter policy makers from moving forward as urgently as they must in order to improve on the ACO model.

The Medicare Shared Savings model, enshrined in the Affordable Care Act (ACA), and the Pioneer program created by the Center for Medicare & Medicaid Innovation (CMMI), are now 3 to 5 years old, if not older. The environment has changed mightily since congressional staffers were crafting the ACO language in the law and contemplating what the political and other realities of that era would tolerate. The conventional wisdom at that time was that both providers and patients would have to be transitioned in a gingerly fashion away from the prevailing model of fee-for-service healthcare. And above all, no policy maker wanted to run the risk of a political backlash from beneficiaries who felt that they were being pried away from their regular doctors—or locked into new care models of unproven quality.

The clear result is that the ACO models established by law, or those created by CMMI, don't have enough carrots or sticks built in to spark dramatic change. And the radically different landscape that has emerged with full-blown ACA implementation suggests

that it is time to put a stronger set of incentives in place.

Policy makers should begin with sizable carrots to entice beneficiaries to sign on with ACOs and agree to tighter limits on care. CMMI should mount an experiment in which beneficiaries can obtain discounts on their Part B premiums, or similar financial incentives, if they agree to enroll in tightly managed "narrow network" ACOs. With nearly 1 in 3 Medicare beneficiaries now enrolled in Medicare Advantage plans, it's clear that many enrollees have grown comfortable with preferred provider or even HMO-style networks. And despite concerns being voiced about the narrow networks in many health plans available on new health insurance exchanges, a recent Kaiser Health Tracking Poll shows that these plans hold appeal for enrollees who are most concerned about holding down costs.[2]

It is well worth testing whether beneficiaries with financial "skin in the game" would be more inclined to see their healthcare more actively managed by an ACO. Such organizations would affiliate with hospitals, nursing homes, and other providers that fully understand that the goal is not necessarily just to shift care from one venue to another, but to provide care in the most cost-effective setting. It is hard to believe that beneficiaries and ACOs with these more clear-cut incentives would produce results as muddy as those found in the first-year Pioneer evaluation. And if they did, we would pretty much know then that reinventing US healthcare was a hopeless effort.

Clearly, at least a part of America's largely dysfunctional policy-making apparatus has some appetite for further change. A small bipartisan group of US Senators and House members recently unveiled the Better Care, Lower Cost Act, which would expand the use of multidisciplinary health teams to coordinate care for Medicare enrollees with multiple chronic conditions.[3] Under their proposal, health plans and providers would create "Better Care Plans" or "Better Care Practices," which would be paid on a risk-adjusted, capitated basis and rewarded for producing better health outcomes for beneficiaries. As currently proposed, enrollment would be voluntary. But this is just the type of experiment that could be made far bolder and potentially more effective if beneficiaries had substantial financial incentives to sign up.

When it comes to making permanent changes in the trajectory of Medicare spending, more "small collective impact" isn't what the nation needs. Big collective impact, with beneficiary buy-in, is.

Author Affiliations: Susan Dentzer is the senior policy advisor for the Robert Wood Johnson Foundation.

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Four Key Competencies for Physician-Led Accountable Care Organizations

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The idea of aligning payer, provider, and patient interests around the 3-part aims of better health, better care, and lower costs is at the heart of the accountable care movement. In its most fundamental form, an accountable care organization (ACO) creates financial incentives for providers to try to reduce the total healthcare expenditures for a panel of patients while at the same time improving quality and patient experience metrics. Unlike the unpopular managed care reforms of the 1990s, which focused on achieving cost reductions through limiting patient choice and access to services, the ACO movement seeks to achieve cost savings by providing the most appropriate care for each patient—ultimately resulting in higher-quality care—and in many cases, the patient is not restricted in their choice of providers and services. While these factors introduce greater difficulty in achieving savings compared with managed care, an increasing number of provider organizations are taking on this challenge, at least in part due to the belief that the modern information and data tools that have transformed our economy could be brought to bear in healthcare.

The meaningful use of electronic health records (EHRs) and the structures put into place for patient-centered medical homes form a critical infrastructure for accountable care, but they are not sufficient. In this article, we describe 4 technology-dependent areas of innovation that we believe are key to the success of ACOs. At the Brookings ACO Learning Network, over 17 physician-led ACOs are working together in small teams to implement 1 or more of these new competencies, and through an open dialogue, they are sharing their experiences with other workgroup members such that all can benefit from these "experiments" in health delivery. We intend to present the preliminary results of these "Innovation Exchanges" at the National ACO Summit, held June 18-20 in Washington, DC, and hope to publish the key lessons learned from this project in the form of a "road map for physician-led ACOs" later this fall.

1) Risk Stratification: Description → Diagnosis → Prediction → Prescription

The movie recommendations we receive on Netflix, our likelihood of being approved for a loan, our chances of landing a job interview, the advertisements that are targeted to us, how political campaigns speak to us, and in many cases the very screen that loads when we browse an e-commerce website are all customized to us based on a sophisticated analysis of multiple streams of available data, from our historical activities, our social networks, our responses to questions, even the Web browser we use. We are slotted into 1 of a multitude of behavioral segments along multiple dimensions.

By now we are all familiar with the premise of "hot spotting"—the idea that a very small percentage of patients account for the vast majority of dollars spent on healthcare—and that efforts to control costs should focus on managing these patients in a more coordinated fashion. However, it is not enough to focus on patients who are the current high-cost utilizers. Many of these individuals are going through a time-limited crisis which will be resolved without special intervention (for example, a patient with a high-risk pregnancy). For many others, there may be little that can be done to affect the course of illness. What we seek, therefore, is to identify the population of "susceptibles" who are showing a pattern of behavior or characteristics that may indicate impending clinical decompensation and a relative

lack of resilience—both physical and psychosocial. Providers who take accountability for the total cost and quality of care will use data and analytics to move beyond the current paradigm of the "risk score" and toward an incremental progression to understand the different pathways by which our patients fail—and by which we fail them—be they end-of-life agonies, social isolation or family dysfunction, substance abuse, or mental health comorbidities. Such information will not be obtained simply by combing through claims data or the EHR, but instead through more creative approaches such as asking physicians and even patients themselves what barriers and challenges are preventing them from achieving their health goals. Through better understanding of our patients, we can target our care management interventions most appropriately, and with the highest chance of success.

While the concept of using predictive analytics to segment patient populations is not new, ACOs provide an opportunity for significant improvement over prior, often health plan–led "disease management" efforts. The ability to supplement utilization/claims data with clinical impressions and patient interview information collected at the clinic will undoubtedly provide additional predictive power. More critically, the in-person interaction with patients and their caregivers, and the clinical relationship, provide stronger opportunities for effective "prescriptions".

2) Advanced Network Management

While many efforts at quality improvement and practice transformation focus on improving work flows within the practice, ACOs must also be able to create "flight plans" for their patients that ensure they receive high-value care across the care continuum. This includes crafting a network that provides care at the lowest cost/highest value setting, but also creating (and enforcing) expectations with specialists, ancillary providers, hospitals, and postacute providers. These "compacts" may include mutual commitments to operating according to shared care plans, timely electronic communication, and coordinating more closely with the primary care provider. Being able to craft (and prune) a referral network requires analytics that "tier" existing or potential partners on the basis of cost (eg, facility fees) but also utilization patterns (eg, adhering to "Choosing Wisely" appropriateness guidelines). Enforcing these compacts will require the ability to capture and report on metrics relating to expected communication and coordination behaviors.

3) Event Surveillance

ACOs must understand the actual "flight patterns" of their patients outside of their practice. An essential technology that underpins effective accountable care is the capacity to move from retrospective accounting of "leakage" toward prospective surveillance for high-valence events such as emergency department visits and hospital admissions, discharges, and transfers (ADTs). There are a number of different technical resources for obtaining these notifications, from regional or statewide health information exchanges, to direct interfaces from hospital systems, to emerging commercial providers of this service. Needless to say, the form and manner of the notifications will have to be a fit for how the ACO plans to take action; for example, a discharge alert can enable a primary care practice to ensure that every discharged patient has a telephone follow-up within 48 hours and an office visit within 7 days (which would qualify for a $250 "transition in care" payment from Medicare).

4) Patient Outreach and Engagement

A key difference between accountable care and managed care is that patients are not limited to a given provider, and attribution may even be retrospective, as in the Medicare Shared Savings Program. While patients enjoy the freedom to choose their providers, this limits the ability of the primary care provider to "utilization manage" the patient, and introduces the distinct possibility that the patient may migrate their care elsewhere and no longer be attributed to the ACO for savings calculations. Yet, on the other hand, this will incentivize providers to work hard at engaging their patients and making sure that they reach out to patients to bring them in for primary care visits, including wellness visits, which provide an opportunity for crafting a stronger therapeutic relationship. The techniques used by marketers and electioneers to increase the loyalty of customers and their probability of showing up (at the voting booth) therefore become invaluable to healthcare. This is partly based on the application of the hypotheses of behavioral economics, and partly the product of relentless empirical testing (A/B trials).

Successful accountable care will require many types of innovation, and the competencies highlighted in this article are only a few of the challenges facing organizations that have the courage to move away from fee-for-service health delivery. Only time will tell which solutions in each of these areas will be most effective. At the Brookings ACO Learning Network, we are excited to watch how the experiments that are being implemented as part of our Innovation Exchanges play out. The accountable care movement is still in its early innings, but the new financial incentives that align provider, payer, and patient interests can justify the business and technology innovation needed to transform American healthcare.

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IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including XARELTO®, increases the risk of thrombotic events. If anticoagulation with XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

B. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with XARELTO® who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants, *see* Drug Interactions
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Please see Important Safety Information on following pages.
Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events After Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO® to warfarin in clinical trials in atrial fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO® in patients with active pathological hemorrhage.
  - A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable.
  - Concomitant use of other drugs affecting hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and NSAIDs.
- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia)

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO®. The next XARELTO® dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO® is to be delayed for 24 hours.

- **Use in Patients With Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Avoid the use of XARELTO® in patients with creatinine clearance (CrCl) <15 mL/min, since drug exposure is increased. Discontinue XARELTO® in patients who develop acute renal failure while on XARELTO®.

SIX INDICATIONS STRONG

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled
- For the treatment of deep vein thrombosis (DVT)
- For the treatment of pulmonary embolism (PE)
- For the reduction in the risk of recurrence of DVT and of PE following initial 6 months treatment for DVT and/or PE
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee replacement surgery
- For the prophylaxis of DVT, which may lead to PE in patients undergoing hip replacement surgery

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.
- **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO® should discontinue the treatment.
- **Use in Patients With Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO® in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- **Use With P-gp and Strong CYP3A4 Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with combined P-gp and strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan). Avoid concomitant use of XARELTO® with drugs that are P-gp and strong CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort).
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing and is not readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients With Prosthetic Heart Valves:** The safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO® is not recommended in these patients.

DRUG INTERACTIONS

- Avoid concomitant use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.
- XARELTO® should be used in patients with CrCl 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit outweighs the potential risk.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** XARELTO® should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus.

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IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS (cont'd)

There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing.

- **Labor and Delivery:** Safety and effectiveness of XARELTO® during labor and delivery have not been studied in clinical trials.
- **Nursing Mothers:** It is not known if rivaroxaban is excreted in human milk.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Females of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

OVERDOSAGE

- Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of XARELTO® overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable.

ADVERSE REACTIONS IN CLINICAL STUDIES

- The most common adverse reactions with XARELTO® were bleeding complications.

K02X121084JR2

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WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.2, 2.6) in full Prescribing Information, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

B. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**

***[see Warnings and Precautions and Adverse Reactions]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thrombo-prophylaxis *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation: XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1) in full Prescribing Information]*.

Treatment of Deep Vein Thrombosis: XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

Treatment of Pulmonary Embolism: XARELTO is indicated for the treatment of pulmonary embolism (PE).

Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism: XARELTO is indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and/or PE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding *[see Warnings and Precautions]*
- severe hypersensitivity reaction to XARELTO (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including XARELTO, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.2, 2.6) and Clinical Studies (14.1) in full Prescribing Information]*.

Risk of Bleeding: XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents

(tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving rivaroxaban. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may be considered but has not been evaluated in clinical trials.

Concomitant use of other drugs affecting hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions]*.

Spinal/Epidural Anesthesia or Puncture: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

Use in Patients with Renal Impairment: Nonvalvular Atrial Fibrillation: Avoid the use of XARELTO in patients with CrCl <15 mL/min since drug exposure is increased. Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly. Discontinue XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations]*

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population *[see Use in Specific Populations]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations]*.

Use in Patients with Hepatic Impairment: No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations]*.

Use with P-gp and Strong CYP3A4 Inhibitors or Inducers: Avoid concomitant use of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) *[see Drug Interactions]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Drug Interactions]*.

Risk of Pregnancy Related Hemorrhage: In pregnant women, XARELTO should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

Patients with Prosthetic Heart Valves: The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.

ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation *[see Boxed Warning* and *Warnings and Precautions]*
- Bleeding risk *[see Warnings and Precautions]*
- Spinal/epidural hematoma *[see Boxed Warning* and *Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 16326 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 4728 patients who received either XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily (EINSTEIN DVT, EINSTEIN PE) or 20 mg orally once daily (EINSTEIN Extension) to treat DVT, PE, and to reduce the risk of recurrence of DVT and of PE; and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

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Hemorrhage: The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF study.

Table 1: Bleeding Events in ROCKET AF*

Parameter	XARELTO N = 7111 n (%)	Event Rate (per 100 Pt-yrs)	Warfarin N = 7125 n (%)	Event Rate (per 100 Pt-yrs)
Major bleeding†	395 (5.6)	3.6	386 (5.4)	3.5
Bleeding into a critical organ‡	91 (1.3)	0.8	133 (1.9)	1.2
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5
Bleeding resulting in transfusion of ≥2 units of whole blood or packed red blood cells	183 (2.6)	1.7	149 (2.1)	1.3
Gastrointestinal bleeding	221 (3.1)	2.0	140 (2.0)	1.2

* For all sub-types of major bleeding, single events may be represented in more than one row, and individual patients may have more than one event.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding rates excluding strokes are 3.3 per 100 Pt-yrs for XARELTO vs. 2.9 per 100 Pt-yrs for warfarin.

‡ The majority of the events were intracranial, and also included intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and to Reduce the Risk of Recurrence of DVT and of PE: EINSTEIN DVT and EINSTEIN PE Studies: In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 2: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

Parameter	XARELTO† N = 4130 n (%)	Enoxaparin/ VKA† N = 4116 n (%)
Major bleeding event	40 (1.0)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Intracranial	2 (<0.1)	4 (<0.1)
Non-fatal critical organ bleeding	10 (0.2)	29 (0.7)
Intracranial‡	3 (<0.1)	10 (0.2)
Retroperitoneal‡	1 (<0.1)	8 (0.2)
Intraocular‡	3 (<0.1)	2 (<0.1)
Intra-articular‡	0	4 (<0.1)
Non-fatal non-critical organ bleeding§	27 (0.7)	37 (0.9)
Decrease in Hb ≥ 2g/dL	28 (0.7)	42 (1.0)
Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant non-major bleeding	357 (8.6)	357 (8.7)
Any bleeding	1169 (28.3)	1153 (28.0)

* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

EINSTEIN Extension Study: In the EINSTEIN Extension clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1.8% for XARELTO vs. 0.2% for placebo treatment groups. The mean duration of treatment was 190 days for both XARELTO and placebo treatment groups.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN Extension study.

Table 3: Bleeding Events* in EINSTEIN Extension Study

Parameter	XARELTO† 20 mg N = 598 n (%)	Placebo† N = 590 n (%)
Major bleeding event‡	4 (0.7)	0
Decrease in Hb ≥2 g/dL	4 (0.7)	0
Transfusion of ≥2 units of whole blood or packed red blood cells	2 (0.3)	0
Gastrointestinal	3 (0.5)	0
Menorrhagia	1 (0.2)	0
Clinically relevant non-major bleeding	32 (5.4)	7 (1.2)
Any bleeding	104 (17.4)	63 (10.7)

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.
† Treatment schedule: XARELTO 20 mg once daily; matched placebo once daily
‡ There were no fatal or critical organ bleeding events.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N = 4487 n (%)**	**N = 4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N = 3281 n (%)**	**N = 3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N = 1206 n (%)**	**N = 1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.
† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)
‡ Includes major bleeding events

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Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions: Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN Extension study are shown in Table 5.

Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN Extension Study

System Organ Class Preferred Term	XARELTO N = 598 n (%)	Placebo N = 590 n (%)
Gastrointestinal disorders		
Abdominal pain upper	10 (1.7)	1 (0.2)
Dyspepsia	8 (1.3)	4 (0.7)
Toothache	6 (1.0)	0
General disorders and administration site conditions		
Fatigue	6 (1.0)	3 (0.5)
Infections and infestations		
Sinusitis	7 (1.2)	3 (0.5)
Urinary tract infection	7 (1.2)	3 (0.5)
Musculoskeletal and connective tissue disorders		
Back pain	22 (3.7)	7 (1.2)
Osteoarthritis	10 (1.7)	5 (0.8)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	6 (1.0)	2 (0.3)

* Adverse reaction (with Relative Risk >1.5 for XARELTO versus placebo) occurred after the first dose and up to 2 days after the last dose of study drug. Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical adverse reactions, the patient is counted only once in a category. The same patient may appear in different categories.

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

Table 6: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

System/Organ Class Adverse Reaction	XARELTO 10 mg (N = 4487) n (%)	Enoxaparin† (N = 4524) n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication.
† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

Other clinical trial experience: In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of rivaroxaban. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, cytolytic hepatitis

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

DRUG INTERACTIONS

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban exposure.

Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, erythromycin and fluconazole), increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. The increases in exposure ranged from 30% to 160%. Significant increases in rivaroxaban exposure may increase bleeding risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

When data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors *[see Warnings and Precautions]*.

Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Results from drug interaction studies and population PK analyses from clinical studies indicate coadministration of XARELTO with a combined P-gp and strong CYP3A4 inducer (e.g., rifampicin, phenytoin) decreased rivaroxaban exposure by up to 50%. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautions]*.

Anticoagulants and NSAIDs/Aspirin: Single doses of enoxaparin and XARELTO given concomitantly resulted in an additive effect on anti-factor Xa activity. Single doses of warfarin and XARELTO resulted in an additive effect on factor Xa inhibition and PT. Concomitant aspirin use has been identified as an independent risk factor for major bleeding in efficacy trials. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. Coadministration of the platelet aggregation inhibitor clopidogrel and XARELTO resulted in an increase in bleeding time for some subjects *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concurrent use of XARELTO with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions]*.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Patients with renal impairment receiving full dose XARELTO in combination with drugs classified as combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, felodipine, erythromycin, and azithromycin) may have increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected.

XARELTO should be used in patients with CrCl 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit justifies the potential risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus *[see Warnings and Precautions]*.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

Labor and Delivery: Safety and effectiveness of XARELTO during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

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Nursing Mothers: It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue XARELTO, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups *[see Clinical Pharmacology (12.3) and Clinical Studies (14) in full Prescribing Information]*.

Females of Reproductive Potential: Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

Renal Impairment: In a pharmacokinetic study, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Treatment of DVT and/or PE, and Reduction in the Risk of Recurrence of DVT and of PE: In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery: The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Hepatic Impairment: In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

OVERDOSAGE:

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Active Ingredient Made in Germany

Finished Product Manufactured by:
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Enhancing Patient Experience in an Era of "Pay for Experience"

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A national effort to improve the quality of healthcare and lower costs is under way. Supported by a growing body of literature demonstrating that health systems emphasizing the role of primary care can achieve superior outcomes at lower costs,[1] the Patient Protection and Affordable Care Act of 2010—or simply the Affordable Care Act (ACA)—makes a concerted effort to revitalize the foundation of primary care by reforming reimbursement for providers delivering high-value, patient-centered care and rewarding innovative models of healthcare delivery. The accountable care organization (ACO) and the patient-centered medical home (PCMH) have emerged as inter related models for health system reform, with the common objective of improving the quality and coordination of healthcare and slowing the growth of spending. While the provider-led ACO model focuses on managing the complete continuum of care, overseeing quality of care, and controlling costs, the PCMH model emphasizes comprehensive, patient-centered care as well as payment reform via enhanced reimbursement to primary care providers for high performance.[2]

Increasingly recognized as a core element of quality healthcare delivery in the United States and other countries,[3] patient-centered care experiences are gaining prominence. An extensive body of literature supports the notion that patient experience is associated with improved health outcomes and better medication adherence.[4-7] Studies of the PCMH have demonstrated the potential for this model to improve patient experience.[8-10] For the accountable care system to succeed in providing high-value care, primary care plays a vital role. Additionally, new recognition of patient experience has grown as health plans and health systems have begun to link measures of patient satisfaction to provider payment,[7] helping providers and healthcare systems to understand patient perceptions of care delivery and establishing the concept of "pay for experience" in clinical care. At the heart of primary care is the patient-provider relationship, and as "pay for experience" broadens its reach, upholding mechanisms necessary to revitalize patient-provider communication will be necessary to maintain a strong foundation of primary care.[9]

As ACOs expand and practices consider transformation to PCMH models of care, policy makers and leaders of healthcare organizations must consider several key elements in order to improve and sustain patient experience. First, health systems must preserve job "do-ability" in primary care. Second, organizations need to capitalize on patient experience survey data to drive care process improvement across the entire continuum of patient care. Third, these organizations must leverage health information systems to enhance virtual patient communication and disease management.

Physician supply in primary care has been associated with improved health outcomes and reduced mortality.[11] However, the severe shortage in the primary care workforce, coupled with a wave of retiring baby boomers and the ACA's provision of insurance coverage to 32 million new Americans, puts primary care in exceeding demand.[12] Already, there is insufficient time in primary care to provide evidence-based care in the management of chronic disease[13] and the average primary care physician's panel size of 2300[14] is too large to offer optimal care, even assuming team-based care.[15] Physician burnout, startlingly prevalent[16] and known to be associated with decreased patient satisfaction and decreased expression of empathy,[17,18] may escalate as providers find themselves held accountable to "pay for experience" while simultaneously adjusting to new payment models and anticipating new quality metric expectations.[19] Encouragingly, one demonstration of the PCMH had a positive impact on primary care providers' self-reported burnout[8] while also improving patient experience and quality, though longitudinal evidence is needed. Increasing the supply of primary care providers to prevent po-

tential compromises in health outcomes and provider burnout (factors sure to impact patient experience), emphasizing team-based care delivery, and reforming payment policies for primary care physicians and specialists[20] are all essential first steps toward optimizing patient experience.

Patient surveys have been routinely used among innovative physician organizations as a means to assess patient experience. As the Centers for Medicare & Medicaid Services begins to roll out incentives for quality metrics and clinical practice improvement activity,[21] organizations may find increasing value in using patient experience surveys to inform outcomes and care delivery. One recent study demonstrated variability in organizations' use of data gathered from these surveys: over half applied the information toward group wide practice improvement, while less than half targeted low-performing physicians (and a small number of practices did nothing).[22] As organizations consider transforming to a PCMH model of care, examining the perspectives of patients will be essential to ensuring improvements in patient experience. Applying these data across the continuum of patient care—from primary care office visits to specialists, throughout hospitalizations, and encompassing ancillary services—will be a key step toward achieving patient-centered care, recognizing that patient satisfaction is a complex construct reflected in a range of patients' whole-care experiences (eg, accessing care, staff interaction, provider communication and follow-up, among others).[23]

Health information technology (HIT) offers the opportunity to improve patient experience via enhanced patient engagement. Capitalizing on electronic health record (EHR) capabilities to streamline management of chronic diseases and transitions in care make innovative approaches to "virtual" care an important step forward in enhancing patient-centered care in the medical home.[24] For example, EHRs can activate patient engagement by generating real-time after-visit care plans. Patients and providers have both expressed interest in secure e-mail exchange,[25-28] and studies of technology to facilitate safer care transitions have been met with patient enthusiasm.[29] Information exchange is vital to patient-centered communication,[30] and further research on the role that personal health records may play in this process is warranted. Virtual care allows providers and patients to exchange information remotely and asynchronously, such as via a patient Web portal or through tele-health. Compensation for complex care management outside of a primary care office visit is a promising example of recent legislation with the potential to incentivize providers and improve patient experience.[31] Even so, dedicated efforts aimed at narrowing the "digital divide" will be imperative if we are to realize the full potential for HIT to enrich the experiences of all patients.[32]

Robust evidence has established the many downstream effects of positive patient experience. Strengthening the primary care workforce, incorporating patient perspectives into care-process development, and committing to innovative applications in HIT build a foundation upon which the experiences of patients in primary care can thrive. To sustain and enhance patient experience in an era of transformation in care delivery and reimbursement reform where "pay for experience" plays a key role, a combined macro policy-level and micro practice-level approach has the potential to realize continuous, comprehensive, and coordinated primary care as organizations strive to expand access and promote patient-centered care.

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Kathleen Sebelius' Name Is Not On Any Ballot.

But Make No Mistake, This Is Her Campaign

MARY K. CAFFREY

After a disastrous start, the effort to enroll 7 million people on healthcare exchanges under the Affordable Care Act hit its stride in January. With time running short, however, the move is under way to redefine success through the stories of ordinary Americans. It's a classic campaign strategy, and one that new polling shows just may convince voters that a law they still don't like probably should not be repealed.

JERSEY CITY, NJ

Through piles of snow on February 4, 2014, the press turned out. During the presidential interview, Fox News' Bill O'Reilly had pressed President Barack Obama on why Health and Human Services (HHS) Secretary Kathleen Sebelius was still around[1] after the epic fail otherwise known as the launch of HealthCare.gov, which half of US states are using to enroll consumers on the federal exchange under the Affordable Care Act (ACA).[2]

"Why didn't you fire Sebelius?" O'Reilly asked.[3]

The president did not so much answer O'Reilly's question as ignore it, choosing instead to focus on the 3 million who had enrolled for health coverage on the exchanges to that point.[1] (The most recent total is 4 million through February 27, 2014.[4])

The chattering classes have been asking O'Reilly's question since the website's catastrophic launch, especially with estimates of repair costs ranging from $600 million to $1 billion.[5,6] A piece in *The National Journal* on Sebelius's staying power offered reasons from the then—Kansas governor's key 2008 endorsement of Obama to their shared love of basketball.[7]

Frequently overlooked is an obvious, more practical reason: To have any shot of meeting the original goal of signing up 7 million people by March 31, 2014, when the first open enrollment ends, someone had to go out and sell this thing. And from the start, the person with that assignment has been Sebelius.

Two days after the Super Bowl, and 8 weeks before that deadline, Sebelius arrived at City Hall in Jersey City for a stop on what might be the toughest campaign of her life. This effort looks every bit the push to the finish that it is; some in the trenches admit as much. There are campaign stops, targeted groups, talking points, ground troops, and no shortage of barbs at those who have fought Obamacare every step of the way. There's also money, amid fresh speculation in *The Washington Examiner* that Sebelius has not stopped raising funds for Enroll America,[8] the group created to sign up the uninsured from what was left of Obama's last campaign for president.

But as the deadline nears, it seems Sebelius has decided that the 7 million target she had touted as late as September 2013[9] was in fact someone else's creation—the Congressional Budget Office's, to be precise. So, Sebelius has simply moved the goalpost to, well, maybe…nowhere.

"First of all, the 7 million was not the administration. That was a CBO, Congressional Budget Office prediction when the bill was first signed," Sebelius said in a February 25, 2014, interview with HuffPost Live host Marc Lamont Hill. "I'm not quite sure where they even got their numbers. Their numbers are all over the board, and the vice president [Joe Biden] has looked and said it may be closer to 5 to 6."[10]

Sebelius' answer was no accident. *The American Journal of Accountable Care* had asked HHS for the most recent enrollment numbers and how they compared with projections. The day before the HuffPost appearance, an HHS response floated this same claim that the administration never made projections, only the CBO did.

The appearance with Hill was the clearest evidence yet that Sebelius seeks to redefine what victory will look like come March 31. Her Jersey City stop was among the last that focused on the numbers game instead of individual triumphs, what campaigns call "people like me." When HuffPost's Hill, whose interview could hardly be called aggressive, kept pressing Sebelius for a revised goal, she said only, "Everyone who is covered is a success story."[10]

A Campaign Like No Other

So why send out a battered secretary to promote Obamacare? Numbers matter in campaigns, and Sebelius's are stellar. She can lay claim to something even the president cannot: Kathleen Sebelius has faced the voters 8 times in her life, and she has never lost.[11] In her first race for Kansas governor in 2002, the pro-choice Democrat garnered 52.9% of the vote in a red state, with America in war mode. She won reelection in 2006 with 57.8%.[12]

Photo by John McCusker of The New Orleans Advocate

During a February 7, 2014, event to promote the Affordable Care Act in New Orleans, Mayor Mitch Landrieu, left, and US Health and Human Services Secretary Kathleen Sebelius focused on stories of how working class Louisianans found affordable health coverage through the federal exchange.

Her past year belies the fact that Sebelius was once considered one of her party's brightest stars.

In Jersey City, Sebelius's skills as a retail politician were on full display as she warmed up to local officials and took questions from reporters. "Mayors are the hardest working elected officials in the country," she said, in a nod to her host, 36-year-old Steve Fulop. "They're really where the rubber meets the road."[13] Her theme in Jersey City: with 2 months to go, enrollment is climbing, and there's still time to sign up.

When a Cabinet officer serves a chief executive at any level, whether that leader is the president, a governor, or a big-city mayor, the rules of carrying a major policy portfolio are never spoken, yet they are crystal clear: the ball is yours to carry until just before the goal line. When success is assured, the boss carries it across. With the ACA rollout, early missteps—even Obama called them "fumbles" in his Super Bowl interview[1]—meant that Sebelius's task would be the equivalent of scoring after a 30-yard sack on first down. In theory, enrolling 7 million people might still be possible. It would also be really, really hard.

Sebelius's road show was in full swing before enrollment opened October 1, 2013, but her quest screeched to a halt from self-inflicted wounds: the software meltdowns, the president's broken promise of "If you like your plan you can keep your plan," except when you can't.[1] Her low point came on October 30, 2013, when she told the House Energy and Commerce Committee, "You deserve better. I apologize. I'm accountable to you for fixing these problems."[14]

By January 2014, she was back on the road, trying to make up for lost time. The Friday before the Jersey City stop, Sebelius had been in St. Louis, Missouri,[15] telling taxpayers there that they were losing $5 million a day by refusing to expand Medicaid under the ACA. But she also brought out Nathaniel Carroll, a 28-year-old father and law student, who found coverage for $43 a month.[15] On February 7, 2014, came New Orleans, where Sebelius kept her focus off the big picture and squarely on the stories of consumers paying stunningly low out-of-pocket costs for healthcare. "People like me" tales are critical to campaigns. Days are spent hunting down and vetting participants, for these stories are gold: both New Orleans newspapers wrote about the 29-year-old mother paying $17 a month for insurance.[16,17]

In the background are footsteps of the 2014 midterm elections, for which the ACA will be both poster child and piñata. At her New Orleans stop, Sebelius and Mayor Mitch Landrieu reminded everyone that Louisiana's Republican governor Bobby Jindal's refusal to expand Medicaid affects 242,000 residents; Sebelius called on everyone to appeal directly to state legislators to change this fate.[17] Such an outcome is unlikely, but that's not the point.

Mitch Landrieu, fresh off his reelection, joked with the local media that he was still speaking with Sebelius even though she'd hired away his health director, Karen DeSalvo, MD, as national coordinator for health information technology.[17] But the mayor's older sister, US Senator Mary Landrieu (D-Louisiana), facing her own reelection campaign when the ACA is less popular statewide, was nowhere to be seen.[18] Reminding lower-income voters what they are missing because of a Republican governor will not change Jindal's mind, but it might energize the voters that Mary Landrieu needs in November.

Impediments to Enrollment

By conventional measures, Sebelius's outing in Jersey City was successful. The largest daily newspapers based in New Jersey, the *Star-Ledger* of Newark[19] and the *Record* of Hackensack,[20] as well as the local *Jersey Journal,*[13] sent both reporters and photographers to cover the press conference, and all ran stories the next day. A half-dozen radio and Web outlets covered Sebelius as well.

Nothing about the choice of Jersey City was by happenstance: Sebelius's host, Mayor Fulop, is close to the "young invicible" demographic she most needs to enroll and is a friend of the cause. On October 14, 2013, at the height of the website meltdown, the mayor penned a blog on The Huffington Post taking on the naysayers who continued to throw marbles under Sebelius's feet as she tried to bring health coverage to the uninsured.[21] In the piece, Fulop touted a mobile Navigator Program, federally funded with a $400,000 grant,[21] which brought 4 bilingual counselors to one of America's most diverse cities; program representatives were on hand for the event and mingled with the press after Sebelius departed.

Also important is Fulop's embrace of multimedia: he brought his own cameraman from "JCTV," the city's in-house channel; he updated his Facebook feed about the visit; and he shared the news with 7500 Twitter followers.

But as Sebelius answered questions, the scope of her chal-

lenge became evident. In her view, purposeful efforts by some to impede consumers from learning about the ACA have been so profound that some of its basic features—those put in place to create the "affordable" part of the act's name—remain unknown to the very people the law is meant to help.

When asked by *The American Journal of Accountable Care* what she sees as the biggest impediments to getting the uninsured to sign up, Sebelius was blunt: "Misinformation." she said,"If people have never had insurance, they figure it will be unaffordable." To this day, working-class families who are eligible for financial assistance to bring down out-of-pocket costs don't realize what's available to them. When they find out, "That's news to a lot of folks," she said.

There is also a lack of awareness that persons with chronic health problems can now gain access to insurance, perhaps for the first time. "No longer can anyone be locked out because of a pre existing condition," Sebelius said.

Independent polling bears her out: the Kaiser Family Foundation Health Tracking Poll from January 2014, taken just before the Jersey City appearance, showed that while awareness of the implementation of ACA had increased slightly, sizable shares of adults—and even larger shares of the uninsured—still did not know about key provisions of the law.[22]

January's Kaiser data showed that about 4 in 10 adults, and about 5 in 10 uninsured, did not know that the law includes financial assistance to low- and moderate-income families to help them buy coverage, gives states the option to expand Medicaid programs, and prohibits insurers from denying coverage based on pre-existing conditions.[22] Of course, not having information may or may not be due to misinformation.

In Jersey City, Sebelius made a point of mentioning how many New Jersey residents could still sign up for Medicaid. The Garden State is among those with Republican governors, such as Ohio and Arizona, that expanded coverage for lower-income residents but did not create their own exchanges.[2] As February drew to a close, Sebelius was turning up the heat on those Republican governors who had not expanded Medicaid, especially when targeting African American audiences.[10]

Despite her campaign skills, Sebelius's efforts come as Americans are highly distrustful of government messages and messengers. A Gallup poll taken January 5 to 8, 2014, found that 21% of Americans view dissatisfaction with government, politicians, and poor leadership, including abuse of power, as the top problem facing the country. Poor healthcare and its high cost tied for third (with lack of jobs) at 16%.[23]

Most startling, after years of healthcare headlines and furious debate, some basics were lost even on the press corps, whose job it is to pay more attention than the typical uninsured person. Before Sebelius arrived, a radio reporter asked a print columnist who covers healthcare, "So… what's the deadline for this?"

The Ground Game

All modern political campaigns have multiple moving parts. There are the parts seen, represented by the candidate or spokesperson and the media operation; and the unseen, which involves the vast apparatus of identifying and fine-tuning lists of persuadable customers. Most often, these people are converted into votes, and the Obama for America operation was legendary for its ability to slice and dice the electorate[24] and then bring people willing to vote for the president to the polls on Election Day, in what is called "the ground game."

The organization Enroll America, a 501(c)[3], is attempting to do something unprecedented: take the data, people, and know-how of recent voter turnout efforts and use this infrastructure to identify and sign up the uninsured.[25] It's a promising idea, but simple it is not. Voting and enrolling for insurance are vastly different decisions, as the Enroll America canvassers are learning.

Voting, especially in presidential contests, may mean one likes his choice, but it can also mean a person simply dislikes his choice less than the alternative. Long lines aside, the act of voting is brief. And most importantly, it's free. An 18-to-34 year-old—a special focus of this effort—may have to surrender a few minutes of his time to vote, but he does not have to scramble for a car payment or forgo a night out with friends, which might be necessary to buy something ethereal like health insurance.

Enrolling young people is essential to ensure a proper mix in the risk pool. No traditional campaign faces this challenge: even if Sebelius could somehow hit the 7 million mark, she also needs to properly balance the cost of taking care of older, sicker Americans by enrolling sufficient numbers of younger, healthier ones so that rates don't skyrocket in the future.[26] For a politician, this is counterintuitive. Typically, one seeks to run up the numbers where support is easiest to find. Sebelius must ensure that either she or someone else is finding those Americans most skeptical and unwilling to sign up for coverage.

This task is being aided by the "young invincibles," which is not just a description of the demographic that is relatively healthy, relatively broke, and often hard to engage. Young Invicibles is an actual group, started among Washington, DC, law students, some of whom have worked for such liberal luminaries as US Representative Chris Van Hollen (D-Maryland) or the late US Senator Edward M. Kennedy (D-Massachusetts).[27]

But if January brought a respite from Website woes, February brought the reality that time was running out. *The New York Times* story of February 18, 2014, "Obama's Vote-Getting Tactics Struggle to Find the Uninsured,"[28] read like a mushroom cloud to anyone who understands how such operations work. Reporter Michael D. Shear wrote that over 4 hours, 41 canvassers in Broward County, Florida, made contact with 2623 people and signed up just 25.[28] At well under 1 enrollee per canvasser over half a day, the results are, in their own way, as stunning as the early days of HealthCare.gov.

The operation's Florida director directly compared the effort

to reaching voters. "They are going to hear from us multiple times between now and the end of March until they tell us they have insurance," Nicholas Duran told *The Times*. "It's just like a campaign."[28]

The *Times* also revealed the scale of the enterprise: Planned Parenthood is paying 400 people $12 an hour to canvass; Enroll America has hired 266 workers, trained 14,000 volunteers, and raised $7 million to reach the uninsured on the Web.[28] But if this campaign resembles traditional ones in other ways, the *Times* story would likely have had an immediate effect: It could not have been easy to raise money for the cause in the succeeding days.

Another shoe dropped February 19, 2014, when *The Washington Examiner* reported on e-mails that revealed extensive interaction between Enroll America and HHS, including a weekly conference call and encouragement from the nonprofit for Sebelius and her top aides to fund-raise on their behalf.[8]

The next day, Vice President Joe Biden predicted that the final enrollment figure would land between 5 and 6 million, in line with estimates the CBO revised after October's botched launch. After 5 more days, Sebelius herself was backing off even that downgraded forecast, and being lampooned for doing so.[9]

The Road Ahead

Research by the Kaiser Family Foundation and Massachusetts' experience with healthcare reform suggest a final enrollment wave could come: the oldest and sickest sign up first, and the younger and healthier wait until the last minute.[26] HHS data show that the share of 18-to-34 year-olds enrolling in January 2014 was 27%, compared with 24% for the first 3 months. In raw numbers, enrollment on the federal exchange was pulling away from the state exchanges.

Public opinion in the Kaiser tracking poll for February was mixed: half of the uninsured still said they didn't have enough information to understand how the law would affect their families, and a majority of the uninsured (56%) retained a negative view of the ACA.[30] But the poll also found that 56% believe the ACA is here to stay and don't want Congress to repeal it, even though 48% want some changes.[30] An Associated Press account from the February meeting of the National Governors' Association said members at this pragmatic gathering agree that, practically speaking, the ACA won't be repealed.[31]

HHS reports that Sebelius will stay on the road until the end of March, although a spokeswoman declined to say how many cities she would visit or to characterize her activity. Campaign schedules are always in flux. But if the boss starts joining her on the road, it will be a sign that Kathleen Sebelius's numbers are looking brighter.

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A Novel Pharmaceutical-ACO Collaboration:

The Merck/Heritage Provider Network Open Innovation Challenge

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Accountable care is forcing providers to develop new capacities and strategies for managing cost and quality trends. Prospectively managing the health of populations requires shifting the focus of care delivery from episodic interventions to continuous population management. As a result, accountable care organizations (ACOs) are dedicating considerable focus to developing the infrastructure and tools needed to help patients manage their chronic conditions. This is a significant departure from traditional care-delivery models and will require provider organizations to develop new partnerships and embrace new methods.

The enhanced focus on patient outcomes and value for ACOs in general will mean that pharmaceutical companies will have to reshape their relationships with ACOs along these lines. Refocusing these relationships around value will require (1) collaborative measurement of patient outcomes; (2) new commercial models that enable value-based payment; and (3) a broadening of the relationship to develop solutions and services that enhance outcomes independent of the pharmaceutical companies' products. It is this latter requirement that prompted Merck & Co, Inc, a global pharmaceutical company, and the Heritage Provider Network, Inc (HPN), a Southern California based managed care organization with affiliates in Arizona and New York, and the largest of the Pioneer Model ACOs, to engage in a collaborative process to identify novel solutions in disease areas of considerable shared epidemiological interest: diabetes and heart disease. During the fall of 2013, Merck and HPN launched an open innovation challenge around care plan adherence for patients with diabetes and heart disease. To our knowledge, this is the first collaboration between a pharmaceutical company and an ACO.

This article describes this collaboration, the innovation process, and implications for further collaborations between ACOs and other healthcare stakeholders.

Defining the Problem

As we transition to a clinically integrated system that incentivizes quality and better health outcomes, care plans are critical patient engagement tools that will be invaluable in helping patients become informed and educated.

Care plans serve as road maps for patients, because they outline diagnosis and treatment, schedules for follow-up, and vital information and resources postvisit. Additionally, they serve as a lifeline, allowing providers to monitor their patients and ensure coordination among the healthcare team. But there are significant challenges associated with creating and delivering successful care plans between the provider and the patient. More than 40% of patients misunderstand, misinterpret, forget, or ignore healthcare advice given by their providers.[1] Factors associated with patient compliance to provider-recommended care plans include patients' knowledge and understanding of treatment and effective communication between the patient and provider.

HPN has a long history of providing coordinated care, and both Merck and HPN realized that adherence to care plans for patients with chronic diseases is an underutilized lever for improving a patient's quality of life, while also potentially creating cost reductions in healthcare. Together, leadership from the 2 organizations decided to use an open innovation process to identify and incubate ideas that would advance shared aims around improving adherence to care plans for patients with these conditions.

Structure

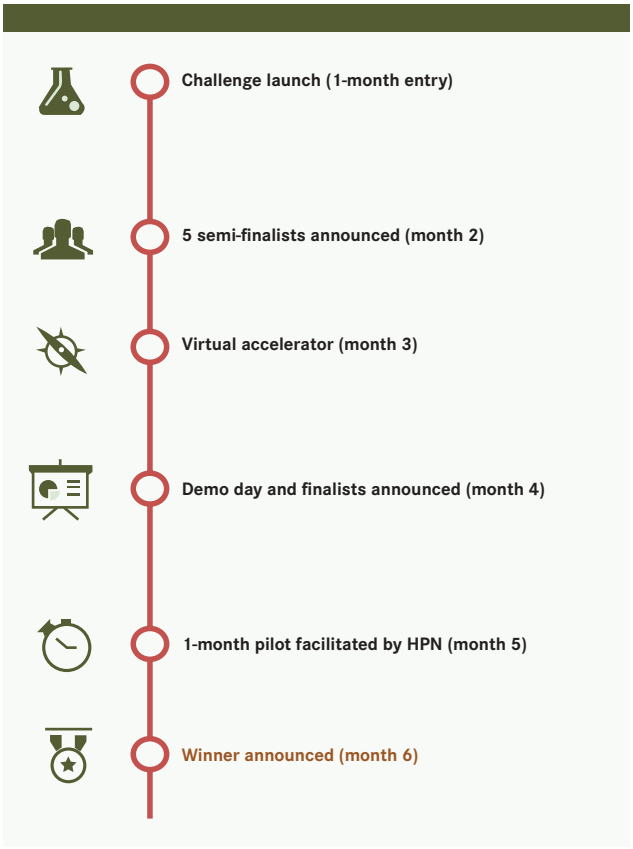
Many sectors have looked to "the wisdom of the crowd" or the phenomenon that the collective knowledge of the community is greater than the knowledge of the individual[2] to devise novel solutions to complicated problems. The use of challenge competitions and an open innovation process to drive breakthrough results has a very long history, going back hundreds of years.[3] For example, Charles Lindbergh's flight across the Atlantic can be traced back to a challenge famously titled The Orteig Prize, a $25,000 reward offered to the first aviator to fly nonstop from New York City to Paris. While this mechanism has been well defined in other sectors, it is relatively new to the healthcare services arena. Challenge-based competitions have proved to be successful frameworks for addressing fundamental research questions by presenting difficult problems and data to the community and enabling the open exchange of ideas and methodologies. Merck and HPN quickly realized that the long-standing problem of treating chronic diseases could benefit from a community approach, and as a result, the 2 organizations collaborated on devising an open innovation challenge competition that aimed to source and incorporate novel care plan products or services to support providers and patients in the area of chronic disease management.[4] (HPN has sponsored a number of other prizes, including prizes related to hospitalization prediction and cancer cell networks, but this is the first nondata, nontechnology challenge in which HPN has participated.)

Table 1. Select Finalist Concepts

CONCEPT	DESCRIPTION
Personalized diabetes coaching	Using a platform that synthesizes work flow, data capture, device integration, and reporting–enabling personalized service delivery via coaches.
Comprehensive patient adherence profiles	Using a personality characteristic database. In a 6-minute session, the platform determines the psychological triggers that will be most effective to attain medical adherence with each patient.
Messaging support via SMS	Crafting interactive conversations so providers can better support patients between appointments. This concept helps providers create and monitor care plans (and thus patient progress) while delivering SMS support.
Care plan reinvention and reformulation	Using mobile devices, artificial intelligence, and human-centered process design. A clinically proven proprietary method of delivering care plans to patients was developed as dynamically generated personalized multimedia daily to-do lists on mobile devices.

Merck and HPN's aim was to apply the best practices of open innovation to identify novel solutions for managing patients with chronic diseases. There has been some experimental research indicating that traditional approaches like "winner-take-all" prizes are suboptimal for generating solutions.[5] We therefore opted for a staged process, with the opportunity for multiple prizes across teams.[6] Additionally, other innovation processes, such as lean methodology and design thinking, were embedded into the structure of the challenge. Drawing on established principles for open innovation challenges, Merck and HPN designed an innovation challenge with several phases.

Figure 1. Overall Challenge Timeline



Challenge Launch and Submission Phase

Outreach is essential for open innovation challenges. Merck and HPN partnered closely with Luminary Labs, an innovation and strategy consultancy, for the operational components of this challenge, and to ensure that the right community of solvers was involved.

Following announcement of the challenge, there was a 1-month open call to the public for submissions. To spread awareness of the challenge and ensure that there would be broad outreach, Luminary Labs notified key media outlets in technology, big data, and healthcare.

Overall, 90 teams submitted solutions for consideration. These submissions spanned from initial concepts to fully mature products or services: 17 in the idea phase, 33 in the early prototype phase, 14 in the full prototype phase, 14 in the beta phase, and 12 that were publicly available. Concepts included hardware, stand-alone care planning solutions, communications platforms, and comprehensive integrated care systems. Eighty-four percent (84%) of submitted solutions were patient-facing; the remaining submissions aimed at multiple segments of the ecosystem. With over 17,000 visits to the challenge website, there was wide-ranging interest and geographic reach. Visitors drew from academic, government, and private-sector spheres that included the Broad Institute, the Bill and Melinda Gates Foundation, Facebook, the Centers for Disease Control and Prevention, and the White House.

Virtual Accelerator & Finalist Selection

An independent panel of judges from the healthcare, innovation, development, and design communities selected 5 teams to proceed on to the virtual accelerator process. Submissions were then evaluated on several dimensions.

The 5 semifinalist teams were composed of clinicians, scientists, patient-entrepreneurs, media producers, and technologists, and the solutions ranged from early prototype to established startup.

Accelerators are designed to support the successful development of entrepreneurial companies and are aimed at increasing the likelihood of success for those companies and iterating their concepts. The 5 semifinalists took part in rigorous design, prototyping, and business modeling sessions tailored to the strengths and weaknesses of each team. The virtual accelerator process consisted of 3 core modeling sessions.

Modeling session 1 focused on an introduction to design thinking also on need-based solution development. These exercises functioned as primers on cultivating empathy, end-user focus, and rapid prototyping. The semifinalists were also exposed to interview-based ethnography, where they simulated exercises in patient engagement and were asked to reconsider care coordination from new angles. The sessions were designed with the patient in mind—

and more specifically, how entrepreneurial companies can refocus their solutions to ensure that patient and provider needs are met.

Modeling Session 2 commenced with a stronger emphasis on patient interaction and learning how to complement technology with disease self-management. Semifinalists met with 2 panels of patients living with diabetes and/or heart disease, and gained insights by simulating the complex experience of learning to live with chronic disease from the perspective of a patient and of a caregiver. Clinicians provided their observations from the field, noting best practices and pain points regarding increasing adherence and patient engagement to improve health outcomes.

Modeling Session 3 gave semifinalists the opportunity to access experts in different fields, ranging from business modeling and capital acquisition to design and public speaking. Teams were provided hands-on mentorship from industry experts and continually crafted their solutions to focus on the problem at hand.

Lessons Learned

Several insights have emerged from this collaboration. First, by placing a dedicated focus on the challenge announcement and community outreach, Merck and HPN were able to develop a landscape view of the marketplace for care plan adherence solutions. The process also gave both parties proximity to the innovator community, opening up a new opportunity for identifying and harvesting talent from a diverse group of forward thinkers offering fresh ideas and a unique perspective. Second, Merck and HPN were able to successfully source solutions that proactively engage patients to promote lifestyle changes around healthy behaviors and medication management, as well as bridge the communication and coordination gap between patients and providers. This collaboration initiative serves as a model for engaging entrepreneurs and key health stakeholders to work across the care continuum.

As we move toward an increased focus on patient engagement, there is an opportunity for organizations to create dynamic and effective programs that facilitate the exchange of information. Shifting to new models will require an increased focus on identifying clinical gaps to uncover every opportunity and implement patient-centric care plans.

CONCLUSIONS

Open innovation, while common in other industries, is still relatively new to the healthcare field. This approach provides a pathway for collaboration, rapid identification of solutions, and access to the broader marketplace. The aim of both Merck and HPN was to apply the best practices of open innovation to identify novel solutions for managing patients with chronic diseases. The quality and quantity of submissions showed notable interest from entrepreneurs to data scientists to clinicians and provided a diverse set of solutions. The challenge allowed both Merck and HPN to look beyond their own walls and gain access to non-traditional partners and products. Additionally, this first-of-its-kind pharmaceutical-ACO collaboration demonstrated how challenge competitions can set in motion communities of innovators to develop sophisticated tools for care management, lay the groundwork for future collaboration, and offer a mechanism for stakeholders like Merck and HPN to collaborate.

Figure 2. Judging Criteria and Constraints

Concept maturity	Early prototype, full prototype, beta, publicly available product/service
Target audience	• People living with diabetes • People living with heart disease • People living with both diabetes and heart disease • Healthcare providers and members of the clinical patient ecosystem (physicans, nurses, pharmacists, etc) • Members of the nonclinical patient ecosystem (family, friends, caregivers, social service providers)
Does concept address the core needs of its target audience?	To what extent does the concept respond to issues that impact care plan success? (eg, life stage, education, familiarity with terminology, support systems, financial and professional circumstances)?
Methodology for design and development	Cascade, design thinking, lean startup, etc
Market readiness	How do you propose to take your concept to market?
Business model	Who will provide funding, how will the concept be distributed, how will engagement be sustained over time, etc?
Is concept data-driven?	What data and analytic aspects are part of the concept?
Probability of success	To what extent will the team's skill sets, experience, and ability to collaborate bring the concept to life?

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Using Payment Reform to Improve the Value of Maternity Care

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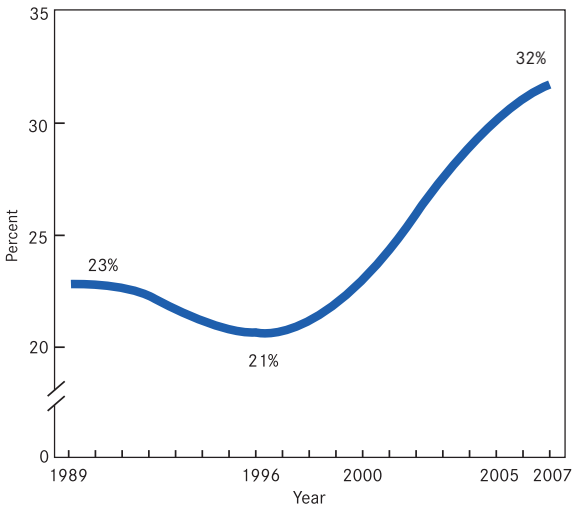
Despite some recent exciting news from The Leapfrog Group about how hospitals have finally achieved lower rates of early elective deliveries, the United States still has a long way to go when it comes to improving maternity care. The rate of early elective deliveries is going down, on average, across the nation, but far too many individual hospitals and specific regions still have unacceptably high rates. The current rate of Cesarean deliveries (C-sections) in the United States has been steadily growing (**Figure 1**), and remains dangerously high at almost 33%[1] (inductions of labor contribute to this rate). Also, there often are built-in financial incentives for unnecessary medical intervention during delivery, which can negatively impact health outcomes for infants. These trends have a profound impact on both society and the economy, resulting in poorer care for an increasingly high price.

Nationwide in 2010, average commercial insurer payments for all maternal and newborn care were $18,329 for vaginal births and $27,866 for C-sections. These payments are approximately 100% more than what Medicaid pays for the same care.[2] From 2004 to 2010, average commercial insurer payments for all maternal care increased by 49% for vaginal births and 41% for C-sections.[2] And from 2004 to 2010, average out-of-pocket payments for all maternity care covered by commercial insurers increased nearly 4-fold for both vaginal births (from $463 to $1686) and C-sections (from $523 to $1948).[2]

Figure 1. Rate of C-section births, United States, 1989 to 2007



The total Cesarean delivery rate is the percentage of all live births by Cesarean delivery.
Source: CDC/NCHS, National Vital Statistics System.

The Power of Payment

We know that how we pay for healthcare creates powerful incentives to healthcare providers to deliver care in certain ways. Today, the financial incentives baked into how we pay for maternity care do a poor job of motivating providers to deliver care that adheres to evidence-based guidelines or to eliminate inappropriate and wasteful services. In fairness, while providers seldom make clinical decisions based solely on how they will be paid, changes to payment methods can compel providers and delivery systems to put new policies and procedures in place to help measure and deliver better care. For instance, "hard stop" policies prohibiting early elective deliveries permit hospitals to stop a physician from admitting a woman for an early elective delivery unless they document the medical necessity of the procedure.

Hence, it is not surprising that changing how we pay for maternity care can improve health outcomes. At our "National 'Virtual' Summit on Maternity Care Payment Reform" held March 3rd, 2014, Catalyst for Payment Reform (CPR) took an in-depth look at a variety of payment models designed to yield desired results.

Models of Risk

The payment models discussed during the Summit represent a spectrum of financial risk for providers. The end of the spectrum with the least risk features "upside only" payments, or payment

reform that gives providers the chance for financial gain with no added financial risk. On the opposite end of the spectrum are models of "downside only" risk, in which providers are at financial risk for needing additional resources to care for a patient. Also included are "2-sided risk" models in which healthcare providers have the opportunity for both financial gains and losses.

Upside Only (Pay-for-Performance)

WellPoint, a Blue Cross and Blue Shield Association managed care company, shared design details about its "upside only" model, called the Quality Insights Hospital Incentive Program (Q-HIP). Under this program, hospitals can earn enhanced fees for meeting metrics related to reducing early elective deliveries, reducing unwarranted C-sections, and reducing healthcare associated bloodstream infections in newborns.

Downside Only (Nonpayment)

BlueCross BlueShield of South Carolina and the South Carolina Department of Health and Human Services (SCHHS), which administers South Carolina's Medicaid system, along with the support of many other stakeholders, partnered to engage providers in quality improvement activities, and then all agreed to stop paying for early elective deliveries. The program, called the Birth Outcomes Initiative, has reduced unwarranted early elective inductions by 50% (**Figure 2**), decreased neonatal intensive care unit admissions, and saved the SCHHS more than $6 million. South Carolina is the first state in the nation in which the Medicaid administrator and the largest commercial insurer have collaborated to establish a policy of nonpayment for early elective deliveries. CPR authored a case study on the Birth Outcomes Initiative late last year.[3]

Two-Sided Risk

Hoag Memorial Hospital Presbyterian (Newport Beach, California) partnered with Blue Shield of California (BSCA) to develop an accountable care organization (ACO) focused in part on improving maternity care. Physicians, the hospital, and BSCA worked together to gather data on practice patterns and outcomes and also put processes in place, including a hard stop for early elective deliveries. When providers achieve goals, they share in the savings; but they also have shared financial risk. Capitalizing on this opportunity, they have realized savings in the millions of dollars and reduced their C-section rate. Hoag and others are now working with the Pacific Business Group on Health on a program that will pay a "blended" payment rate for vaginal and C-section deliveries. The program is designed to incrementally reduce preventable, low-risk, first C-section deliveries to 23.9%, which is a goal of Healthy People 2020, a US Department of Health and Human Services initiative.[4]

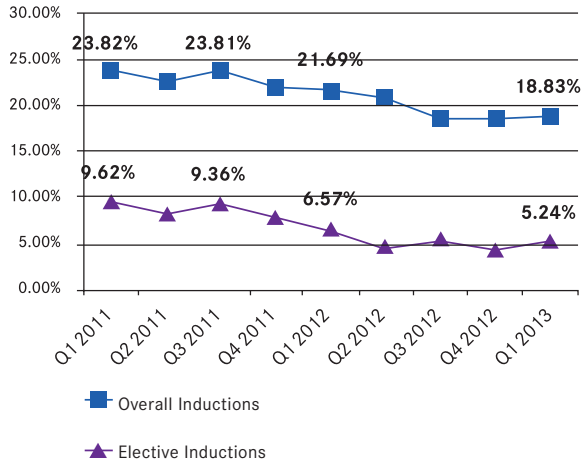
The Employer Perspective

The members of CPR—large employers and other healthcare purchasers that include Medicaid and public employee and retiree agencies—are extremely interested in these types of pilots and programs. Maternity care remains an area of extremely high spend for many large employers and especially for state Medicaid agencies. A recent survey released by Truven Health Analytics found that during the 5-year period of 2006 to 2011, employer healthcare costs increased by an average of 4.3% per year, driven largely by spending on preventive health services: osteoarthritis (except spine); multiple sclerosis; childbirth (C-section); and complications of surgical and medical care.[5]

Aligning with the evidence base and eliminating unnecessary interventions results in better health outcomes and reductions in spending, and employers and other purchasers know this area demands their attention. Employers are also interested in strategies they can use to engage consumers—and that includes expectant mothers. By combining education with information on the quality and price of various providers with financial incentives through benefit and network designs, purchasers and payers can incentivize consumers to seek care from high-value providers, maximizing their own benefits as well as the impact of payment reform models.

Employers are eager to educate consumers about what constitutes high-quality maternity care. Shared decision-making programs can help guide consumers through the options available to them, including whether to seek a C-section during a pregnancy that poses questionable risk. Organizations have created a variety of tools—like the "Less Than 39 Weeks Toolkit" provided by the March of Dimes—designed to educate consumers about the dangers of early deliveries.

Figure 2. Reductions in Early Elective Inductions in South Carolina Following the Implementation of Quality Improvement Efforts and a Nonpayment Policy



Which Model Is Best?

While there isn't a model that will work for every market, CPR's hypothesis is that payment methods may be most powerful when

there is some potential downside financial risk for providers. If this hypothesis holds true, pay-for-performance models will have better results when they morph into "shared risk" arrangements. However, for markets in which providers are unable or unwilling to accept financial risk, an upside-only model may be the only starting place to initiate any change in practice patterns. Steps taken to remove the financial incentives for performing unnecessary intervention during labor and delivery will help align the evidence base with practice, ultimately improving health outcomes for infant and mother as well as helping to contain costs.

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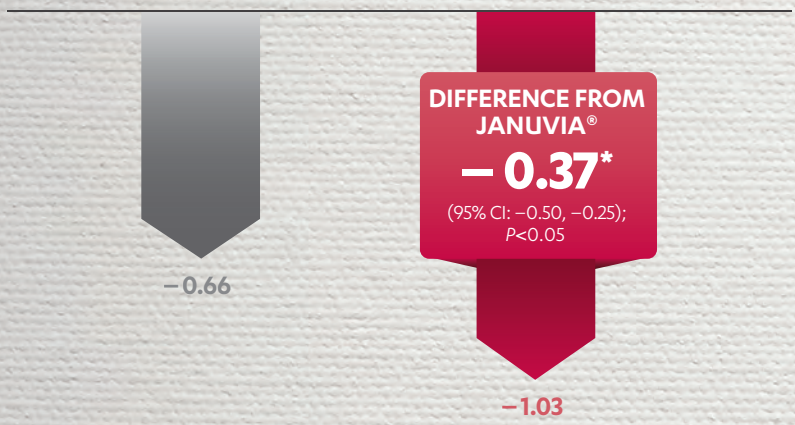

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- **Impairment in Renal Function:** INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

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Adverse Reactions

In 4 pooled placebo-controlled trials, the most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.[1§]

References: 1. INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013. **2.** Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36(9):2508-2515. **3.** Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ. Data as of 9/17/13.

SGLT2 = sodium glucose co-transporter-2.

§Included 1 monotherapy and 3 add-on combination trials with metformin, metformin + a sulfonylurea, or metformin + pioglitazone.

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»**Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.

»**Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.

»**Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.

»**Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.

»**Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

ENVISION NEW
POSSIBILITIES

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.
- **Digoxin:** There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥0.5 times clinical exposure from a 300-mg dose.

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.
- **Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.
- **Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).
- **Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

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»**Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSAGE

»There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

»The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation.

K02CAN13149

Please see brief summary of full Prescribing Information on the following pages.

Invokana™
canagliflozin tablets

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information]*.

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions]*.

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions]*. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA or any other antidiabetic drug.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Impairment in Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to

INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections includes the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg (N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

INVOKANA™ (canagliflozin) tablets

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reactions (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

***** Includes placebo and active-comparator groups

† Patients could have more than 1of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

***** Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions]*.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0

INVOKANA™ (canagliflozin) tablets

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies (continued)

In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including

UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

INVOKANA™ (canagliflozin) tablets

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

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janssen

The Best of Reform:

Postacute Care Bundling

TOM SCULLY, JD; KELSEY MELLARD, MPA

Regardless of the broader controversies, parts of the Patient Protection and Affordable Care Act—also known simply as the Affordable Care Act (ACA) or Obamacare—are working. As a result, the Centers for Medicare & Medicaid Services (CMS) is introducing new demonstrations. Specifically, within the Medicare population, there is a new focus on the quality and cost of postacute care (PAC). PAC consists of skilled care, therapy, and other services provided by home health agencies (HHAs), skilled nursing facilities (SNFs), inpatient rehabilitation facilities (IRFs), and long-term care hospitals (LTCHs). *PAC is currently one of the least structured parts of the healthcare delivery system.* Briefly, by the numbers, PAC is increasingly part of the healthcare spend conversation:

- A recent report published by The Associated Press-NORC Center for Public Affairs Research suggests that the population of those over age 65 will nearly have doubled by the time the last baby boomers turn 65.[1]
- The Institute of Medicine recently reported:
  - If regional variation in PAC spending did not exist, Medicare spending variation would fall by 73%.
  - 43% of Medicare patients utilize PAC services following a hospitalization.
  - 23% of total medical spending is spent on PAC.
  - Medicare spending on PAC grew at 8% annually from 2001 to 2012.
  - In 2013 alone, Medicare spending for PAC services exceeded $62 billion.[2]

The primary initiative focused on utilization and transparency of outcomes within PAC is the Bundled Payment for Care Improvement (BPCI) initiative from the Center for Medicare & Medicaid Innovation (CMMI). Our company, naviHealth, a PAC benefit manager, is participating with a handful of the hospitals engaged in BPCI. Specifically, naviHealth is a convener for Model 2: Retrospective Acute & Postacute Care, and is partnering with 5 health systems that span across 5 states.

Background on BPCI

The CMMI was created as part of the ACA, and has produced several models to advance the bipartisan support of bundled payments. Regardless of political affiliation, the bundled payment programs—the ultimate bundle being Medicare Advantage—offer significant improvement over the current Medicare fee-for-service payment structure. Incentives and penalties are driving providers to manage beneficiaries beyond the 4 walls of the acute-care setting.

Bundling of payments allows Medicare to align incentives for all providers, across the continuum, based on an agreed-upon episode of care. Providers are responding by producing significantly better outcomes. Bundled payment for care improvement consists of 4 models:

1. *Retrospective Acute-Care Hospital Stay Only.* The episode of care is defined as the inpatient stay in the acute care hospital.
2. *Retrospective Acute-Care Hospital Stay Plus Postacute Care.* The episode of care includes the inpatient stay in the acute hospital, all related services during the episode, and either 30, 60, or 90 days after the hospital discharge. Participants can select up to 48 different clinical condition episodes.
3. *Retrospective Postacute Care Only.* The episode of care is triggered by an acute-care hospital stay and will begin at the initiation of postacute care services with a participating SNF, IRF, LTCH, or home health agency for 30, 60, or 90 days. As with Model 2, participants can select up to 48 different clinical condition episodes.

4. *Acute-Care Hospital Stay Only.* The episode will be based on a selection of 48 clinical conditions, and CMS will make a single, prospectively determined bundled payment to the hospital that encompasses all services during the inpatient stay by the hospital, physicians, and other practitioners.

Under Models 1, 2, and 3, Medicare will pay the hospital an agreed-upon discounted rate based on the payment amount established under the Inpatient Prospective Payment System (IPPS) used in the original Medicare program. Medicare will continue to pay physicians separately for their services under the Medicare physician fee schedule. Part of the retrospective reconciliation includes an opportunity for hospitals and physicians to share gains arising from the providers' care redesign efforts. Under Model 4, physicians and other practitioners will submit "no-pay" claims to Medicare and will be paid by the hospital out of the bundled payment. Related readmissions for 30 days after hospital discharge will be included in the bundled payment amount.

naviHealth as a Convener

On January 1, 2014, naviHealth and our 11 partner hospitals launched our BPCI program in the following markets: Dignity Health in San Bernardino, California; Lovelace Health System in Albuquerque, New Mexico; Hillcrest Healthcare System in Tulsa, Oklahoma; Saint Thomas Health in Nashville and Murfreesboro, Tennessee; and Lourdes Health System in Camden, New Jersey. In coordination with each of these partners, our care managers will coordinate care for qualifying beneficiaries (based on clinical condition) for 90 days after their acute hospital discharge.

While the acute-care stay and discharge planning is part of the episode, the 90 days following the acute discharge is where naviHealth utilizes more than a decade of experience with almost a million patients to meaningfully change the behavior and outcomes for Medicare beneficiaries. In partnership with the hospital, we identify the beneficiary by day 2 of their acute stay, if not prior to their acute stay (identification prior to acute stay is easier for elective surgeries), and begin the dialogue about their projected PAC needs. We will provide an evidence-based road map to the beneficiary and caregivers on how to navigate the upcoming transitions of care, ensuring that the patient is in the right setting and receives the right intensity of care, for the right amount of time, to improve patient satisfaction and patient outcomes, and at a lower cost.

Continual evaluation and management of the beneficiary's care plan ensures the delivery of the most appropriate care. We are targeting a subset of 48 clinical conditions (surgical and medical), staffing accordingly, and partnering with PAC providers to enhance the coordination features. An episode consists of a "bundling" of diagnosis related groups (DRGs) related to a like clinical condition. Eligible beneficiaries must fall within one of the clinical episodes and be enrolled in Medicare Part A and B. They can be a dual-eligible enrollee (Medicare and Medicaid) as long as Medicare is the primary payer, and they cannot have an identified diagnosis of end-stage renal disease (ESRD) or be enrolled in a Medicare Advantage plan.

The Role of the Care Managers

As part of our care coordination approach, we have hired and trained over 150 care managers, who are trained RNs, LPNs, PTs, OTs, and social workers, and will be partnering at the acute-care level to impact the discharge process as well as follow the beneficiary for the 90 day continuum postdischarge. Prior to discharge, and in conjunction with the hospital discharge planning process, the care manager will perform a "live safe," which is naviHealth's predictive technology tool to inform the discharge process based on function score (basic mobility, applied cognition, and daily living skills). We also have a series of risk-screening assessment tools that help us predict the likelihood of a readmission, which provides us information with which to tailor the intensity of our interventions, based on the beneficiary's needs. These interventions are delivered telephonically or face-to-face in the beneficiary's home, or in an acute or PAC setting.

The creation and execution of a care plan that can be modified along the continuum allows for continual calibration of our care managers' interventions and beneficiary contact. Our care managers have undergone several orientations, including hospital orientation and introductions to the PAC providers in their respective market. We believe this level of integration will drive our partnerships and is critical to our success. To build the PAC network in each market, we hosted town hall meetings and invited PAC providers to learn about BPCI and meet our staff, who will be making rounds in their facilities to ensure the beneficiary is achieving functional improvement. We consistently collect data to inform the creation of a severity-adjusted dashboard, allowing us to identify the top-performing PAC providers based not only on efficiency, but also quality. *We are high "touch" and high tech.*

Retrospective Reconciliation of the Payments

As mentioned above, under Model 2, the hospitals will continue to bill under the traditional IPPS, and there will be a retrospective reconciliation of savings accrued. Part of our contract with CMS includes a guaranteed savings to CMS, and any savings accrued on top of the guaranteed amount to CMS will be split among naviHealth and our provider partners. naviHealth will impact the total cost of care within an episode by reducing readmissions and employing our evidence-based methods to identify the most appropriate PAC setting and services to be delivered for an entire episode of care.

What Is the Future of Bundled Payments?

In Washington, DC, we have seen an increase of activity around a broader and more permanent adoption of bundled payments. Recent activity includes the introduction of bipartisan legislation, the Comprehensive Care Payment Innovation Act, in December 2013 by Congressional representatives Diane Black (Tennessee) and Richard Neal (Massachusetts) and, in January 2014, David McKinley (West Virginia) introduced the Bundling and Coordination Post-Acute Care Act of 2014. The Medicare Payment Advisory Commission (MedPAC) has also strongly urged adoption

of new payment models to manage PAC spending while improving the quality of care. In February 2014, CMMI announced the opportunity to expand the current BPCI initiative, with the ability to add episode initiators and episodes. And, on March 4, 2014, President Obama released his Fiscal Year 2015 budget proposal, which included the implementation of bundled payment for PAC providers, starting in 2019, and would account for a projected savings of $8.7 billion. The recent savings projection will make it increasingly likely to be used as a "pay-for" for physician payment form.

With all of this activity, it is not a matter of if, but rather when. CMS just needs to take the time to thoughtfully define the payment methodology, and private payers will follow. Regardless of political affiliations, bundled payments are a step in the right direction. They are happening—the reform is inevitable.

We close with a story from one of our case managers regarding the most important part of these new payment and delivery models—*positively impacting the lives of beneficiaries:*

One of our care managers called one of the Medicare beneficiaries enrolled in our BPCI program to confirm an upcoming follow-up home visit appointment during lunch hour the following day. The beneficiary's daughter is a nurse and resides next door. Our care manager arrived at the home, approached the front door (which is glass), and could see the beneficiary slumped over in his recliner. Our care manager knocked hard on the door, but the beneficiary did not answer or acknowledge our care manager's arrival. Because the care manager had confirmed the appointment and the door was unlocked, our care manager proceeded to enter the home. The beneficiary was not breathing and our care manager was unable to resuscitate him. Given that the daughter was at work, our care manager proceeded to call the ambulance. The beneficiary's blood sugar was 23. Upon dispensing glucose, the beneficiary became conscious again, and the family was very grateful that a care manager was there to check on him.

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Author Disclosures: The authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

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Value-Based Insurance Design: Infusing Clinical Nuance Into Healthcare Transformation

KADEN MILKOVICH AND KATIE SULLIVAN

With the passage of the Patient Protection and Affordable Care Act—or simply the Affordable Care Act (ACA)—came opportunity, including the opening of the federal and state health insurance exchanges, which offer health plan options for millions of Americans. But there have also been challenges, as states continue to debate expansion of their coverage options, including Medicaid and Medicare. While the "law of the land" has provided a much-needed framework for policy changes in the United States, there is still much work to be done to shift healthcare from a volume-based system to a value-based system. To enact this shift, multistakeholder and bipartisan political experts recognize that value-based insurance design (V-BID) is essential to a high-performing healthcare delivery system.[1]

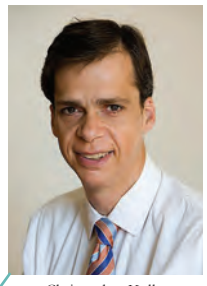
Since its inception in 2005, the University of Michigan Center for Value-Based Insurance Design (V-BID Center, www.vbidcenter.org) has led efforts to promote the development, implementation, and evaluation of innovative health benefit designs that balance cost and quality. Led by faculty that includes *The American Journal of Managed Care*'s co-editors A. Mark Fendrick, MD, and Michael Chernew, PhD, the V-BID Center aligns patients' out-of-pocket costs with the value of health services to deliver high-quality, cost-effective care while encouraging a shift from volume- to value-based insurance benefits and payment models, using the V-BID–defined tenet of *clinical nuance*. Clinical nuance recognizes that (1) medical services and providers differ in the amount of health produced, and (2) the clinical benefit derived from a specific service depends on the consumer using it, who provides it, and where it is delivered.

These concepts and more were highlighted at the V-BID Center's 2013 Summit, "Volume to Value: Infusing Clinical Nuance Into Healthcare Transformation" held on October 8 and 9. The V-BID Center invited policy makers, state health commissioners, plan directors, and health system leaders to engage in a highly interactive format to address supply–and–demand-side innovations in numerous payer settings including state health insurance exchanges, Medicaid and Medicare plans, accountable care organizations (ACOs), and commercial insurance plans.

Dr Fendrick, director, V-BID Center; John Ayanian, MD, MPP, director, University of Michigan Institute for Healthcare Policy and Innovation; and Martin Philbert, PhD, Dean, University of


A. Mark Fendrick, MD


John Z. Ayanian, MD, MPP


Christopher Koller


John Selig

Michigan School of Public Health, welcomed and encouraged attendees to apply the day's discussion to a larger framework of healthcare system redesign. The trio asked that participants frankly share successes and challenges experienced across multisystem reform efforts so that all in attendance might benefit from this "all teach, all learn" opportunity.

Narratives From State Health Leaders

As state-administered health plans respond to health reform requirements, many state health plan leaders have implemented initiatives that draw on the V-BID tenet of clinical nuance as a way to control budget expenditures and improve care delivery across public and private payer systems. The keynote panel, "Narratives from State Health Leaders," moderated by Christopher Koller, president, The Milbank Memorial Fund, featured Bill Hazel, MD, secretary, Virginia Department of Health and Human Resources; Anthony Keck, director, South Carolina Department of Health and Human Services; and John Selig, director, Arkansas Department of Health and Human Services, who offered perspective and examples of translating the "volume into value" concept into action in their respective states.

Dr Hazel remarked that Virginia utilizes benchmark programs such as the American Board of Internal Medicine's "Choosing Wisely" (http://choosingwisely.org/) initiative, which encourages discussion and promotes incentives for both providers and patients to take a closer look at tests and procedures which may be unnecessary. To improve care delivery, he added that Virginia plans to address issues such as end-of-life quality, premature birth rates, consumer engagement, care coordination, and workforce trends such as how to improve the medical education framework to increase the development of necessary providers in primary care and general medicine. Meanwhile, Mr Keck said that although there is "no silver bullet" to solve the healthcare crisis, South Carolina is refocusing efforts on those who are most in need—Medicaid enrollees, in particular. In addition to incentivizing providers to innovate patient care and promote patient engagement, South Carolina is focusing on prioritizing and customizing care delivery to populations in need in order to strategically address care disparities and outcomes. Finally, Mr Selig shared that his state is driven by the motive to "never waste a good crisis." Arkansas state leaders collaborated extensively with providers and legislators and concluded that they could either stick with the status quo—which only temporarily controlled costs without addressing gaps in care or health disparities—or, they could look to more innovative and collaborative forms of healthcare delivery, such as those found in the patient-centered medical home and ACOs that address comprehensive patient health. Overall, Mr Koller summarized, these 3 state leaders exemplified the nonpartisan innovation and collaboration necessary to address healthcare issues at the state level.

Innovations in State Employee Health Plans

State employee health plans comprise a large and complicated percentage of state budgets. As states face infrastructure updates and looming deficits, state benefit plan administrators face a critical need to transform these plans so that enrollees can achieve better health while significantly reducing expenditures. Joan Kapowich, administrator, Oregon Educators and Public Employees' Benefit Boards (PEBBs), and Kevin Lembo, state comptroller, Connecticut, offered remarks on how their states have attempted to address these concerns. Ms Kapowich noted that the PEBB program and the Oregon Educators Benefit Board (OEBB) offer evidence-based care to 275,000 lives, with a patient-centered focus that promotes health, accountability, sustainability, and better outcomes. Both PEBB and OEBB serve as early leaders in value-based benefit design, providing free health screenings, tobacco cessation programs, weight management programs, and chronic care medications/office visits for conditions like asthma, diabetes, and heart conditions. Value-based benefits, Ms Kapowich shared, are linked to patient decision-making support modules that encourage provider communication and disincentivize overutilized care or low-value services. By making health management and wellness a joint effort between providers and patients, these benefit boards have linked personal responsibility and communication to better health and wellness.

Meanwhile, in Connecticut, Mr Lembo offered a review and dashboard data assessment of a V-BID plan the state offered employees beginning in 2012. The Connecticut Health Enhancement Program (HEP) incorporates V-BID concepts that target preventive care and chronic disease management through voluntary enrollment programs, required age-appropriate preventive screenings, lower copayments for medication/care for chronic diseases, and chronic disease management education programs. Other benefits include reduced monthly premium shares and the waiving of annual deductibles. Prior to 2012, Connecticut's state employee health plan did not distinguish between high-value ser-


Anthony Keck


Joan Kapowich


Kevin Lembo


Stephen Fitton


Seema Verma

vices and low-value services in determining cost-sharing for beneficiaries. Currently, specified guideline-based clinical services are required of HEP enrollees with diabetes, high cholesterol, high blood pressure, heart disease, asthma, and chronic obstructive pulmonary disorder. There are provisions to exempt enrollees with unusual or special circumstances from requirements as appropriate. Beneficiaries may be unenrolled from HEP if they do not adhere to the requirements, but can re-enroll by completing outlined compliance requirements of prevention screenings and care management. HEP strives to improve patient compliance via regular reminders and other forms of consumer outreach. Compliance with requirements is verified through claims data when possible, and written personal attestation when claims-based verification is not possible. A year into the program's implementation, compliance is steady and costs are neutral. Through a variety of consumer and provider initiatives, both states are working to supply value-added plans that provide high-quality care and services at an affordable cost to members while incentivizing payers and providers to coordinate delivery of those plans.

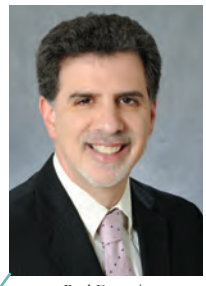
Adding Clinical Nuance to Medicaid

The Centers for Medicare & Medicaid Services' "2012 Actuarial Report on the Financial Outlook for Medicaid" reported that over the next decade, Medicaid expenditure rates are expected to increase at an average annual rate of 6.4%, reaching $795 billion by 2021.2 Additionally, the average enrollment of beneficiaries is expected to increase at an average annual rate of 3.4%, meaning there will be an estimated 77.9 million Medicaid enrollees by 2021.1 As such, the third Summit panel offered insights on how states must address the conundrum of rising enrollee eligibility and increased service delivery needs juxtaposed against decreasing provider networks to address unsustainable costs in public safety-net programs. Seema Verma, founder of the health policy consultancy firm SVC, Inc; Stephen Fitton, director, Michigan Medicaid; and Nick Macchione, director, County of San Diego Health and Human Services Agency, offered examples of how state- and county-based Medicaid programs are responding to these significant challenges. Opening the discussion, Ms Verma discussed the Healthy Indiana Plan, a Medicaid plan that covers uninsured, nondisabled adults aged 19 to 64 years who are below 200% of the federal poverty level (FPL), and who have no access to employer-sponsored insurance and/or remain uninsured for 6 or more months. In accordance with ACA requirements, Healthy Indiana participants have no-cost access to $500 of preventive services and an $1100 deductible. In conjunction with Indiana state contributions, participants must contribute 2% to 5% of their gross income to a "POWER" health savings account to cover the $1100 deductible. Unspent POWER funds can be rolled over in order to reduce contributions used to cover preventive services if the $500 contribution has been reached. Healthy Indiana provides coverage to targeted populations in need and stresses personal responsibility and patient engagement while allowing participants the flexibility to apply their contribution where it is most needed. Relatedly, Stephen Fitton, director, Michigan Medicaid, discussed the recent vote to expand the state's Medicaid program. The new plan—Healthy Michigan—incorporates V-BID language into the plan design and allows the state to enroll eligible nondisabled adults aged 19 to 64 years with incomes between 100% and 133% of the FPL into a contracted health plan that provides a health savings account, into which money from any source can be deposited to pay for incurred health expenses, including, but not limited to, copays. Enrollees with annual incomes between 100% and 133% of the FPL will contribute no more than 5% of their annual income for cost-sharing requirements, waive contributions for the first 6 months of enrollment, and required contributions used to pay for incurred health expenses shall be limited to 2% of annual income. Additionally, the inclusion of V-BID principles in the Healthy Michigan plan will help provide coverage to an additional 470,000 residents over the next several years.

Addressing Medicaid programs at the county level, Mr Macchione said that San Diego has seen "lots of opportunity" with Medicaid reform with an "all-policies approach." Using "horizontal integration" and "silo-busting" tactics, Mr Macchione's administration manages the most expensive and complicated beneficiaries in San Diego County who are dually eligible for Medicare and California's Medicaid program—Medi-Cal—to address multiple chronic conditions and poor care coordination in order to improve continuity of care across acute care, long-term care, behavioral health, and home- and community-based services. By providing a framework of transition care coaches, nurses, personalized technology, and caregiver engagement, Mr Macchione believes we can "treat the cause" of healthcare system problems, not just the illness. He notes that San Diego's goal is


Nick Macchione


Lonny Reisman, MD


Paul Fronstin


Bill Hazel, MD


Dennis Scanlon, PhD

to create an accountable care community that rebalances services in the home and community rather than in institutional settings.

Health Plan Innovation: Lessons Learned

Health insurance plan innovation is not a concept invented by the ACA, but 3 Summit panelists—Paul Fronstin, director, Health Research and Education Program, EBRI; Lonny Reisman, MD, chief medical officer, Aetna; and Dennis Scanlon, PhD, professor of Health Policy and Administration, Penn State University—agree that the law provides all the more incentive for states to look at what they are doing to improve value in plan design. Dr Reisman stated that the "one size fits all" approach in healthcare service pricing and care delivery is not only obsolete, but ineffective. Providers must look to more individualized ways to engage with patients in order to drive medication adherence and improve treatment outcomes and consumer education and engagement. He noted that Aetna has invested in a variety of technology services that drive medication adherence and regimens by trying to find the patients that fall through the cracks of the system. Dr Reisman also spoke about the need for plan designers to be at the forefront of health improvement innovation initiatives, to drive innovation in system wide benefit plan design. Following this discussion, Dr Scanlon provided an interesting scenario of how ignoring or devaluing consumer consent can lead to problematic plan implementation. Describing the controversy that surrounded the Penn State Wellness Plan—which originally levied a $100 monthly non compliance fee on employees who declined to fill out an online health questionnaire, citing the survey as a privacy violation (the fee has since been suspended)—Dr Scanlon queried how similar ACA initiatives that tie wellness compliance to disincentives will affect consumer engagement. Overall, he noted, the rationale and logic used in communication is important to designing incentives that actually work to inspire adherence.

The V-BID Center offered its 2013 Summit, "Volume to Value: Infusing Clinical Nuance into Health Care Transformation," in direct response to national- and state-based reform initiatives (largely as a result of the ACA) to address rapidly expanding healthcare payment and quality reform and expansion efforts. As reform initiatives unfold, the V-BID Center is committed to providing unbiased assistance to those involved in national- and state-based reform efforts. It is our expectation, through collaborative dialogues and frank discussions, that Summit participants have taken away valuable implementation examples to provide effective, responsive care that can be utilized immediately. Contextualizing the role of V-BID across supply-and-demand–side initiatives enables stakeholders to employ V-BID as one of many tools to improve healthcare quality and lower costs as these large-scale infrastructure changes evolve.

To access video and slides of the day's discussion, please go to: http://www.sph.umich.edu/V-BIDcenter/events/2013summit_materials/2013_index.html.

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ACO and Emerging Healthcare Delivery Coalition

Background

As ACOs and other emerging delivery and payment models evolve and move away from traditional fee-for-service system models towards cost-effective and value-based care, the need to understand how these models will evolve is critical to building long term strategic solutions. The mission of the coalition is to bring a diverse group of key stakeholders together, including ACO providers, payers, IDNs, specialty pharmacy and pharmaceutical manufacturers to work collaboratively to build solutions and improve the quality and overall outcomes of patient care.

Coalition Goals

- Gather insights of current "real-world" best practices and strategies for care management interventions
- Gather insights of current ACO physician challenges and best practices in executing successful ACOs, as well as new healthcare delivery models, including the impact of incentive structures for ACO providers–implementation strategies and measurement
- Identify operational lessons and best practices, including key components of transitions-of-care programs; patient and physician engagement; quality measures; formulary decisions; and protocol development.
- Translate key findings into actionable solutions for key stakeholders

Key Stakeholders

- ACO Providers
- Payers
- Integrated Delivery Networks
- Specialty Pharmacy
- Pharmaceutical Manufacturers

Deliverables

- **Participation in two live working group sessions with coalition members:**
  - Free registration for live interactive meeting with Industry leaders across ACOs, payers, IDNs, specialty pharmacy and pharmaceutical manufacturers
  - Opportunity for exclusive breakout sessions with coalition members
- **Two virtual meetings with coalition members - free registration**
- **Ongoing collaboration opportunities with coalition members:**
  - Monthly executive interchanges with thought leaders (includes Q&A)
  - Active participation and proprietary questions in pulse surveys
- **Complimentary subscriptions:**
  - The *American Journal of Managed Care*
  - The *American Journal of Accountable Care* quarterly publication
  - **ACO and Emerging Healthcare Delivery Coalition** newsletter
- **Additional discounts:**
  - Free registration to The *American Journal of Managed Care* live events
  - Discount on HRA syndicated managed care studies and inclusion of 5 proprietary questions in 2014
- **Company/brand advertisements:**
  - The *American Journal of Managed Care*
  - The *American Journal of Accountable Care* quarterly publication
  - **ACO and Emerging Healthcare Delivery Coalition** newsletter
- **Expedited peer review for submissions to AJAC**
- **Additional Resources:**
  - Development of training modules: live, on-line, etc
  - Development of patient education
  - Access to ACO portal resource center within AJMC.com

AJMC's **ACO and Emerging Healthcare Delivery Coalition** is the premier managed care alliance for ACOs, payers, IDNs, specialty pharmacy and pharmaceutical companies. This coalition provides the platform for diverse stakeholders to collaborate and interact regarding the current and evolving healthcare delivery models–to build strategies and solutions, in addition to developing enduring materials to ensure continuous engagement and innovation for all alliance members.