

Panel Endorses Some Pharmacogenomic Tests

BY SUE DARCEY

A few pharmacogenomic tests have been shown to help improve patient outcomes, but most clinical studies of genetic and protein-based tests have not supplied sufficient data on outcomes to guide medical care, members of a Centers for Medicare and Medicaid Services advisory panel concluded.

“Clinical utility is where it’s at, and if

we can’t make good clinical decisions based on test data, then [that data] is useless,” said panelist Dr. Nora Janjan of the M.D. Anderson Cancer Center at the University of Texas, Houston, voicing frustrations expressed by a majority of the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) after hearing an Agency for Healthcare Research and Quality (AHRQ) presentation on the quality of clinical studies.

The panel as a whole expressed reasonable confidence in three tests:

► HER-2/neu assays for breast cancer treatment.

► BCR-ABL assays for diagnosing and monitoring chronic myelogenous leukemia (CML).

► K-RAS gene testing for guiding drug choice in metastatic colorectal cancer.

The committee expressed low confidence in CYP2D6 gene testing (for ex-

ample, Roche’s AmpliChip) to guide tamoxifen treatment of breast cancer, UGT1A1 assays for selecting doses of Pfizer’s colon cancer drug Camptosar (irinotecan), and pharmacogenomic tests based on the BCR-ABL gene to identify point mutations in CML patients.

HER-2/neu protein assays, the most well-established of the lot, are considered necessary prior to treating breast cancer patients with Roche’s Herceptin (trastuzumab). “We believe that it has had a huge impact, already ... for improving health outcomes by pinpointing those who need the drug, and by avoiding toxic therapy in those who don’t,” said Dr. Daniel F. Hayes, an oncologist at the University of Michigan, Ann Arbor.

HER-2/neu assays are widely available via both laboratory methods and Food and Drug Administration–approved kits

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made by Abbott, Bioview, Genetix, Life Technologies/Invitrogen, and others.

K-RAS has received increased attention in recent years, and validation from the American Society of Clinical Oncology, as an aid to choosing colorectal cancer patients to be treated with Eli Lilly/Bristol-Myers Squibb’s Erbitux (cetuximab) or Amgen’s Vectibix (panitumumab).

Despite the vote of confidence, some panelists said they would like to have seen more clinical evidence on the benefits and harms of K-RAS tests.

Dr. Thomas Trikalinos, a researcher at Tufts University, Boston, who presented the AHRQ review, said his team could not find studies of potential harms of K-RAS assays. Genzyme and Qiagen are among the firms with K-RAS assays, but no K-RAS kits have been approved by the FDA, according to agency staff at the meeting.

Industry speakers at the meeting decried Medicare’s slowness in covering such tests, pointing out that many are already in clinical use. Steve Brotman, a senior vice president with AdvaMed, said that although the industry group supports evidence-based decision making, “providing evidence on genetic tests is challenging,” and “isolating the impact of tests on health outcomes is very difficult.”

MedCAC Chairman Clifford Goodman, a senior vice president with the Lewin Group, noted that the meeting was intended “to help shine a light toward science and new technology that will improve patient outcomes.” That goal requires “substantial rigorous evidence” and not “just guesses based on sensitivity and specificity.”

LIPITOR® (Atorvastatin Calcium) Tablets

Brief Summary of Prescribing Information

CONTRAINDICATIONS: Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. Hypersensitivity to any component of this medication. **Pregnancy—**Women who are pregnant or may become pregnant. LIPITOR may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of LIPITOR use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. LIPITOR SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, LIPITOR should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations* in full prescribing information]. **Nursing mothers—**It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require LIPITOR treatment should not breastfeed their infants [see *Use in Specific Populations* in full prescribing information].

WARNINGS AND PRECAUTIONS: Skeletal Muscle—Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with LIPITOR and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, combination of ritonavir plus saquinavir or lopinavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPITOR and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see *Drug Interactions* (7)). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration*, *Drug Interactions*, *Clinical Pharmacology* in full prescribing information].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clarithromycin, itraconazole, HIV protease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20mg atorvastatin daily. The lowest dose necessary should be used.

LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Liver Dysfunction—Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Limit of Normal Values—**Limit of normal values for ALT and AST are 3 times the upper limit of normal (ULN) for ALT and 2 times the ULN for AST. **Incidence of Abnormalities in Serum Transaminases—**Incidence of abnormality in ALT or AST in clinical trials was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of LIPITOR. It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semianually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with LIPITOR. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of LIPITOR is recommended. LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of LIPITOR [see *Contraindications* in full prescribing information]. **Endocrine Function—**Statins interfere with cholesterol synthesis and therefore might inhibit and/or gonadal steroid production. Clinical studies have shown that LIPITOR does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spiro lactone, and cimetidine. **CNS Toxicity—**Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was treated in a similar condition for 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg/day dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. **CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Use in Patients with Recent Stroke or TIA—**In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where LIPITOR 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo (5.2, 2.3% atorvastatin vs. 3.3, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group [see *Adverse Reactions* in full prescribing information].**

ADVERSE REACTIONS: The following serious adverse reactions are discussed in greater detail in other sections of the label: Rhabdomyolysis and myopathy [see *Warnings and Precautions* in full prescribing information], Liver enzyme abnormalities [see *Warnings and Precautions* in full prescribing information]. **Clinical Trial Adverse Experiences—**Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies 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. In the LIPITOR placebo-controlled clinical trial database of 16,066 patients (8,755 LIPITOR vs. 7,311 placebo; age range 10-93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on LIPITOR and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with LIPITOR that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%). The most commonly reported adverse reactions (incidence \geq 2% and greater than placebo) regardless of causality, in patients treated with LIPITOR in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%). Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in \geq 2% and at a rate greater than placebo in patients treated with LIPITOR (n=8755), from seventeen placebo-controlled trials.

Table 2. Clinical adverse reactions occurring in \geq 2% of patients treated with any dose of LIPITOR and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

*Adverse Reaction \geq 2% in any dose greater than placebo

Other adverse reactions reported in placebo-controlled studies include: *Body as a whole:* malaise, pyrexia; *Digestive system:* abdominal discomfort, eructation, flatulence, hepatitis, cholelithiasis; *Musculoskeletal system:* musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system:* transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hypoglycemia; *Nervous system:* nightmare; *Respiratory system:* epistaxis; *Skin and appendages:* urticaria; *Special senses:* vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)—In ASCOT [see *Clinical Studies* in full prescribing information] involving 10,305 participants (age range 40-80 years, 13% women, 94.8% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed race) treated with LIPITOR 10 mg daily (n=5,188) or placebo (n=5,117), the safety and tolerability profile of the group treated with LIPITOR was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)—In CARDS [see *Clinical Studies* in full prescribing information] involving 2838 subjects (age range 30-77 years, 32% women, 94.3% Caucasians, 3.1% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with LIPITOR 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)—In TNT [see *Clinical Studies* in full prescribing information] involving 10,001 subjects (age range 29-78 years, 19% women, 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with LIPITOR 10 mg daily (n=5006) or LIPITOR 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.5 years. Persistent transaminase elevations (\geq 3 x ULN twice within 4-10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK ($>$ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)—In IDEAL [see *Clinical Studies* in full prescribing information] involving 8668 subjects (age range 26-80 years, 18% women; 93.3% Caucasians, 0.4% Asians, 1.1% Blacks, 0.04% other) treated with LIPITOR 80 mg/day (n=4439) or simvastatin 20-40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)—In SPARCL involving 4731 subjects (age range 21-92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 1.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with LIPITOR 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.5 years, there was a higher incidence of persistent hepatic transaminase elevations (\geq 3 x ULN twice within 4-10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK ($>$ 10 x ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions* in full prescribing information].

In a post-hoc analysis, LIPITOR 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 LIPITOR vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (58 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) LIPITOR vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality, 216 (9.1%) in the LIPITOR 80 mg group vs. 213 (9.1%) in the placebo group. The proportion of subjects who experienced cardiovascular death were numerically smaller in the LIPITOR 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced noncardiovascular death were numerically larger in the LIPITOR 80 mg group (5.0%) than in the placebo group (4.0%).

Postmarketing Experience—The following adverse reactions have been identified during postapproval use of LIPITOR. 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.

Adverse reactions associated with LIPITOR therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, hepatic failure, dizziness, memory impairment, depression, and peripheral neuropathy.

Pediatric Patients (ages 10-17 years)—In a 26-week controlled study in boys and postmenarchal girls (n=140, 91% male, 9% female; 93.3% Caucasians, 1.6% Blacks, 1.6% Asians, 4.9% other) the safety and tolerability profile of LIPITOR 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies* in full prescribing information and *Use in Specific Populations*, *Pediatric Use* in full prescribing information].

OVERDOSAGE: There is no specific treatment for LIPITOR overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance LIPITOR clearance.

Please see full prescribing information for additional information about LIPITOR.

Ⓢ only

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