

FDA acts on cancer drug shortages

PARTIALLY IN response to recent shortages of such critically needed cancer drugs as doxorubicin hydrochloride liposomal injection (Doxil) and methotrexate, the FDA has issued draft guidance on detailed requirements for both mandatory and voluntary notifications to the agency of issues that could result in a drug shortage or supply disruption of a prescription drug or biological product.

On October 31, 2011, the FDA sent a letter to manufacturers to raise awareness of the importance of early notification of drug shortages or supply disruptions. According to the agency, the annual number of such shortages tripled from 61 in 2005 to 178 in 2010. Of particular concern were medications that are manufactured by a small number of firms and for which no good substitutes exist.

To address the recent Doxil shortage, the FDA approved temporary importation of another doxorubicin hydrochloride liposomal injection. The agency handled the methotrexate shortage in part by expediting review of the application for a preservative-free formulation of the agent.

Under current regulations, the sole manufacturer of a drug that is deemed life-supporting, life-sustaining, or intended for use in the prevention of a debilitating



disease or condition is required to notify the FDA at least 6 months prior to discontinuing manufacture of the product in question. However, in 2010, only 8% of drug shortages were attributable to permanent discontinuances of the product: The majority of shortages resulted from problems at the manufacturing facility, delays in manufacturing or shipping, and shortages in active pharmaceutical ingredients. In addition, some biological products are vulnerable to shortages but are not subject to mandatory reporting. Under current law manufacturers are not required to report to the FDA the majority of situations that could lead to a drug shortage, and the agency has begun strongly encouraging companies to voluntarily report any issues that could lead to a shortage of any prescription drug

Temporary importation of another doxorubicin hydrochloride liposomal injection and expediting review of a preservative-free methotrexate were actions taken to alleviate recent shortages.

or biological product supplied in the United States.

Approximately 4 months after sending the awareness-raising letter to manufacturers, the FDA registered a sixfold increase in voluntary notification by industry of potential shortages, and distributed a draft guidance for industry on requirements for notifying the agency of a discontinuation of certain drug products (*Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage*).

Whereas all permanent discontinuances of production must continue to be reported to the FDA, the agency is now also asking for even temporary interruptions to be reported if the interruption can reasonably be expected to lead to a disruption in supply of the product. In the draft guidance, the FDA urges manufacturers to be over-inclusive when determining whether the product is life-supporting, life-sustaining, or is used for a debilitating disease or condition, and to be similarly liberal when determining whether they are a sole manufacturer. But the agency is encouraging notification even when companies are not the sole manufacturer of a drug or biological product, and is encouraging voluntary notification for all prescription drug and biological products.

Comments and suggestions regarding this draft document should be submitted to the FDA by May 29, 2012. (Submission information is included in the document.) ■

FDA has begun strongly encouraging companies to voluntarily report issues that could lead to a shortage of any prescription drug or biological product.

Virtual colonoscopy is an accurate screen in seniors

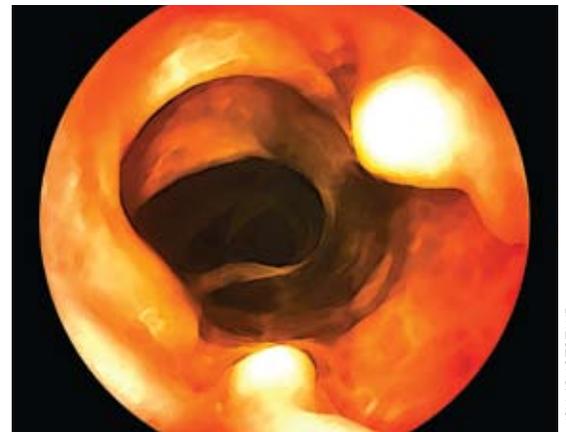
COMPUTERIZED tomographic (CT) colonography, also known as virtual colonoscopy, accurately detects cancer and precancerous polyps in persons aged 65 years and older, indicate the results of a secondary analysis involving participants from the National CT Colonography Trial.

In 2008, C. Daniel Johnson, MD, MMM, of Mayo Clinic Arizona in Scottsdale, and colleagues recruited 2,600 asymptomatic persons aged 50 years and older, who were at average risk for colorectal cancer, to compare non-invasive CT colonography with colonoscopy in detecting the disease. Screening CT colonography

identified adenomas or cancer measuring at least 10 mm in diameter in 90% of participants (*N Engl J Med.* 2008;359[12]:1207-1217).

More recently, Johnson's team compared the sensitivity and specificity of CT colonography in participants of the earlier trial who were younger and older than 65 years. The difference between senior-aged participants and those younger than 65 years was not statistically significant for most measures.

Of 2,531 evaluable enrollees from the original study, complete data were available for 477 participants aged 65 years and older. A total of 33 (6.9%) of these patients had adenomas of 1 cm or



3D virtual colonoscopy showing polyposis of the colon.

larger, compared with 76 (3.7%) of the 2,054 younger patients. For large neoplasms, mean estimates for CT colonography sensitivity and specificity for the older group were 0.82 and 0.83, respectively. Sensitivity and specificity for large neoplasms among the younger participants were 0.92 and 0.86, respectively. ■

ACP issues new colorectal screening guidance

AVERAGE-RISK adults should be screened for colorectal cancer starting at age 50 years, and high-risk adults at age 40 years or 10 years younger than the age at diagnosis of the youngest affected relative, according to a new guidance statement from the American College of Physicians (ACP) (*Ann Intern Med.* 2012;156:378-386).

The new document calls for clinicians to perform individualized risk assessments for colorectal cancer in all adults. Risk factors include increasing age; race (African Americans have the highest incidence and mortality rates for colorectal cancer in the United States); personal history of polyps, inflammatory bowel disease, or

The new document calls for individualized risk assessments for colorectal cancer in all adults.

colorectal cancer; and family history of colorectal cancer.

Once a patient is assessed, the clinician should follow the above-stated age guidelines for screening initiation. The ACP also advises discontinuing screening in adults older than 75 years and in adults with a life expectancy of less than 10 years.

Average-risk patients should be screened for colorectal cancer using a stool-based test, flexible sigmoidoscopy, or optical colonoscopy, and high-risk patients should undergo optical colonoscopy. However, counsels the ACP, tests should be selected based on the benefits and harms as well as availability, and also should be based on patient preferences.

When choosing a stool-based test, clinicians may not want to use fecal DNA tests based on a recent white paper issued by the Agency for Healthcare Research and Quality (AHRQ). After conducting a review, the agency determined that insufficient evidence exists to support using fecal DNA tests to screen adults at average risk of colorectal cancer. AHRQ calls for further research on the effectiveness of fecal DNA testing compared with other stool-based screening tests (AHRQ Publication No. 12-EHC022-EF, www.effectivehealthcare.ahrq.gov/ehc/products/282/971/CER52_Fecal-DNA-Testing_FinalReport_20120229.pdf). ■

Cancer hospitalizations rated

THE AGENCY for Healthcare Research and Quality (AHRQ) released Statistical Brief #125 Cancer Hospitalizations for Adults, 2009. The brief presented data from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample on hospital stays for cancer care among adults age 18 years and older in 2009 (Table 1). Cancer was the principal diagnosis in one-quarter of the 4.7 million cancer-related hospitalizations among US adults in 2009. Adult hospital stays principally for cancer account for approximately 6% of adult inpatient hospital costs. This number decreased by 4% between 2000 and 2009. The growing number of outpatient cancer treatment options may account for some of the decrease in the number of hospitalizations.

The most common hospitalizations for cancer among adult men

Adult hospital stays principally for cancer account for about 6% of adult inpatient hospital costs.

were for prostate cancer, secondary malignancies (such as metastatic disease), and lung cancer. Data in this report indicated hospitalizations for kidney cancer increased 40% between 2000 and 2009, whereas hospitalizations for colon cancer and bladder cancer decreased 14% and 12%, respectively, during the same time period.

The most common cancer hospitalizations among adult women were for secondary malignancies, breast cancer, and lung cancer. Hospitalizations for lung cancer, uterine cancer, and ovarian cancer remained relatively stable from 2000 to 2009. Hospitalizations for all other common cancers decreased; most notably, the data show a decrease of 28% and 26% in hospitalizations for breast cancer and cervical cancer, respectively.

For the full report, go to <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb125.jsp>. ■

On-site lab reduces repeat surgeries

A NEW service at the University of Michigan (U-M) Comprehensive Cancer Center in Ann Arbor, Michigan, has helped reduce the number of women who need additional surgery after an initial resection for breast cancer.

U-M's intraoperative pathology consultation service puts pathologists in the surgical suite to assess tumors and lymph nodes immediately after removal. The surgeon and patient remain in the operating room until the results come back, and any additional surgery can be performed immediately.

A team led by Michael S. Sabel, MD, reported in *The American Journal of Surgery* that among 271 patients evaluated in the 8 months before the facility established the intraoperative pathology consultation service, the average number of surgeries per breast cancer patient was 1.5. Eight months after the service was initiated, that average fell to 1.23 among 278 patients.

The number of patients requiring one surgery increased from 59% in the 8 months prior to implementation of the service to 80% 8 months after, and reexcisions were reduced from 26% to 9%. Frozen section allowed 93% of node-positive patients to avoid a second surgery for axillary lymph node dissection.

Cost analysis indicated a savings of \$400 to \$600 per breast cancer patient, even when accounting for fewer axillary lymph node dissections. ■

TABLE 1. Top 10 most frequent cancer hospitalizations for adults, in 2009^a

Type of cancer	Number of stays (thousands)	Type of cancer	Number of stays (thousands)
Men		Women	
Prostate	97	Secondary malignancies	120
Secondary malignancies	97	Breast	87
Bronchus, lung	79	Bronchus, lung	71
Colon	48	Colon	51
Kidney and renal pelvis	28	Uterine	40
Bladder	28	Ovarian	26
Rectum and anus	25	Cervical	22
Head and neck	24	Rectum and anus	19
Non-Hodgkin lymphoma	23	Non-Hodgkin lymphoma	18
Leukemias	22	Pancreatic	18

^a Data include hospital stays with a principal diagnosis of cancer.

Source: Anhang Price R, Stranges E, Elixhauser A. *Cancer Hospitalizations for Adults, 2009*. HCUP Statistical Brief #125. Rockville, MD: Agency for Healthcare Research and Quality; 2012.

A second gene may predispose women to breast cancer

SCIENTISTS have discovered yet another gene that may advance the mission of *BRCA1*, and even act on its own to help breast cancer develop. The *Abraxas* gene has become a candidate for yet unexplained susceptibility to breast cancer. Recent research has shown it to directly interact with *BRCA1* and contribute to the DNA damage associated with *BRCA1*. In the study, 125 breast cancer families were screened for *Abraxas* mutations. One such mutation, R361Q, was found in breast cancer patients from three of the families, but not in any of the more than 800 healthy controls included in the analysis.

The researchers demonstrated that R361Q blocks *BRCA1* and other proteins from effectively repairing damaged DNA in cells. The mutated *Abraxas* gene appears to increase susceptibility to breast cancer, even in the absence of *BRCA* mutations. The *Abraxas* mutation may also predispose people to other cancers.

On the basis of its exclusive occurrence in familial cancers, its disruption of critical *BRCA1* functions, and other factors, the authors conclude that *Abraxas* mutations connect to cancer predisposition (*Sci Transl Med.* 4[122]:122ra23). Women with *Abraxas* mutations potentially could have chemotherapy or radiation treatment specifically designed to target DNA repair deficits in those mutated cells. ■

Diagnosis delayed for certain cancers and certain patients

A LARGE STUDY conducted in the United Kingdom uncovered a wide variation between cancer types in the proportion of patients who had visited their general practitioner (GP) 3 times or more before being referred to the hospital for cancer diagnosis. The data also revealed that women, young people, and non-whites are less likely to be referred before completing at least three visits with their family doctors.

The analysis focused on 41,299 patients (representing 24 different cancers) participating in the 2010 National Cancer Patient Experience Survey in England. Half the patients who eventually received a diagnosis of multiple myeloma (939 of 1,854 [50.6%]) had three or more visits with their GPs before receiving a referral. Many persons in whom pancreatic cancer was eventually diagnosed also had three or more visits to their primary care provider before being referred to the hospital for diagnosis (193 of 467 [41.3%]).

In contrast, only 7.4% (625 of 8,408) of patients with breast cancer and 10.1% (113 of 1,124) of those with melanoma made three or more prereferral visits to the GP.



Patients aged 16 to 24 years were more than twice as likely as those aged 65 to 74 years to have three or more prereferral visits.

Georgios Lyrtzopoulos from Cambridge University, Cambridge, United Kingdom, and coinvestigators also reported in *The Lancet Oncology* that study participants with a subsequent diagnosis of stomach cancer or lung cancer were among those more likely to have made three or more prereferral visits, whereas men with testicular cancer or women with endometrial cancer were more likely to have been referred to the hospital for diagnosis after only one or two consultations with a GP.

Patients aged 16 to 24 years were found to be more than twice as likely as those aged 65 to 74 years to have three or more prereferral GP visits. The only cancers without an apparent age gradient were testicular cancer and mesothelioma.

Women were less likely than men to be referred quickly for diagnosis, particularly when bladder cancer was the diagnosis. Asians and blacks were less likely than whites to be sent to the hospital after just one or two visits with the GP.

These findings may help health care professionals prioritize early-diagnosis initiatives based on particular cancers and sociodemographic patient characteristics. ■

MOST EXPENSIVE CANCER HOSPITAL STAYS

\$40,200

Leukemia

\$28,700

Multiple myeloma

\$24,900

Non-Hodgkin lymphoma

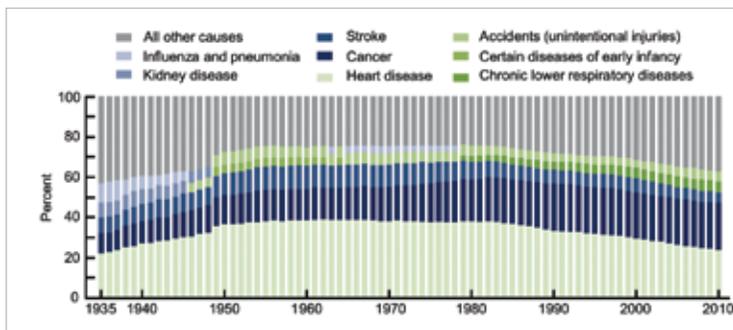
Source: Statistical Brief #125. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; February 2012.

NCHS DATA BRIEF REPORTS ...

Cancer and heart disease cause fewer deaths, but still among top causes

A 75-year perspective from the CDC National Center for Health Statistics shows heart disease and cancer remained among the five leading causes of death between 1935 and 2010. However, the proportion of deaths caused by these two conditions decreased. In 1983, they accounted for 60% of all deaths; in 2010, they constituted 47% of all deaths.

Heart disease and cancer remained the 1st and 2nd leading causes of death, respectively, over the 75-year period.

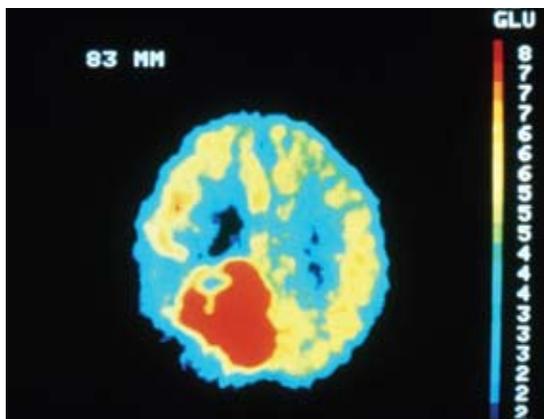


Source: Hoyert DL. 75 years of mortality in the United States, 1935-2010. NCHS data brief, no. 88. <http://www.cdc.gov/nchs/data/databriefs/db88.pdf>. Accessed March 18, 2012.

PET/CT changes brain tumor treatment plans

ADDING FINDINGS from positron emission tomography (PET)/computed tomography (CT) imaging, using the radiopharmaceutical ^{18}F -DOPA, to other diagnostic data prompted physicians to change their original management recommendations for almost half of patients with known or suspected brain tumors. These results suggest that imaging amino acid transporters such as ^{18}F -DOPA (3,4-dihydroxy-6-F-18-fluoro-L-phenylalanine) have a potentially important role in the management of persons with brain tumors.

In the study, published in *The Journal of Nuclear Medicine* (2012;53[3]:393-398), referring physicians were asked to complete a pre-PET/CT survey relating to 58 consecutive patients with known or suspected brain tumors. The survey posed questions about indication, tumor histology or grade, level of suspicion for



tumor recurrence, and planned management.

After obtaining PET/CT imaging studies, the physicians completed a second questionnaire as to whether the imaging findings should be categorized as negative, equivocal, or positive. The participants were also asked to report their level of suspicion for primary or recurrent brain tumors and intended management changes prompted by findings on

Malignant brain tumor (red) seen on PET scan

the scan. A third questionnaire, completed 6 months after PET/CT, was designed to determine patient outcome (recurrence and survival).

Of the 58 cases included in the study, clinical suspicion for recurrence increased in 33%, remained unchanged in 50%, and decreased in 17% after the PET/CT result was added to the available diagnostic data. A total of 26 patients experienced recurrence; the remaining 32 had stable disease or remained disease-free.

Intended treatment changes were precipitated by ^{18}F -DOPA PET/CT findings for 41% of the patients. The most frequent changes were from wait-and-watch to chemotherapy (six patients [25%]), and from chemotherapy to wait-and-watch (four patients [17%]). Additional follow-up revealed that 75% of the intended treatment changes were implemented. ■