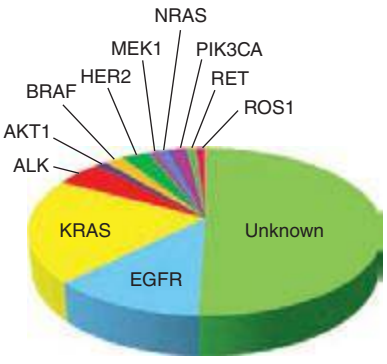

Frequency of driver mutations in NSCLC	
AKT1	1%
ALK	3–7%
BRAF	1–3%
EGFR	10–35%
HER2	2–4%
KRAS	15–25%
MEK1	1%
NRAS	1%
PIK3CA	1–3%
RET	1–2%
ROS1	1–2%

FIGURE 107-2 **Driver mutations** in adenocarcinomas.

appropriately. For example, one set of mutations involves EGFR, which belongs to the ERBB (HER) family of protooncogenes, including *EGFR* (ERBB1), *HER2/neu* (ERBB2), *HER3* (ERBB3), and *HER4* (ERBB4). These genes encode cell-surface receptors consisting of an extracellular ligand-binding domain, a transmembrane structure, and an intracellular tyrosine kinase (TK) domain. The binding of ligand to receptor activates receptor dimerization and TK autophosphorylation, initiating a cascade of intracellular events, and leading to increased cell proliferation, angiogenesis, metastasis, and a decrease in apoptosis. Lung adenocarcinomas can arise when tumors express mutant *EGFR*. These same tumors display high sensitivity to small-molecule EGFR TK inhibitors (TKIs). Additional examples of driver mutations in lung adenocarcinoma include the GTPase *KRAS*, the serine-threonine kinase *BRAF*, and the lipid kinase *PIK3CA*. More recently, more subsets of lung adenocarcinoma have been identifed as defined by the presence of specific chromsomal rearrangements resulting in the abberant activation of the TKs ALK, ROS1, and RET. Notably, most driver mutations in lung cancer appear to be mutually exclusive, suggesting that acquisition of one of these mutations is sufficient to drive tumorigenesis. Although driver mutations have mostly been found in adenocarinomas, three potential molecular targets recently have been identified in squamous cell lung carcinomas: *FGFR1* amplification, *DDR2* mutations, and *PIK3CA* mutations/*PTEN* loss (Table 107-1). Together, these potentially "actionable" defects occur in up to 50% of squamous carcinomas.

A large number of tumor-suppressor genes have also been identified that are inactivated during the pathogenesis of lung cancer. These include *TP53*, *RB1*, *RASSF1A*, *CDKN2A/B*, *LKB1* (*STK11*), and *FHIT*. Nearly 90% of SCLCs harbor mutations in *TP53* and *RB1*. Several tumor-suppressor genes on chromosome 3p appear to be involved in nearly all lung cancers. Allelic loss for this region occurs very early in lung cancer pathogenesis, including in histologically normal smoking-damaged lung epithelium.

EARLY DETECTION AND SCREENING

In lung cancer, clinical outcome is related to the stage at diagnosis, and hence, it is generally assumed that early detection of occult tumors will lead to improved survival. Early detection is a process that involves screening tests, surveillance, diagnosis, and early treatment. Screening refers to the use of simple tests across a healthy population in order to identify individuals who harbor asymptomatic disease. For a screening program to be successful, there must be a high burden of disease within the target population; the test must be sensitive, specific, accessible, and cost effective; and there must be effective treatment that can reduce mortality. With any screening procedure, it is important to consider the possible influence of *lead-time bias* (detecting the cancer earlier without an effect on survival), *length-time bias* (indolent cancers are detected on screening and may not affect survival, whereas aggressive cancers are likely to cause symptoms earlier in patients and are less likely to be detected), and *overdiagnosis* (diagnosing cancers so slow growing that they are unlikely to cause the death of the patient) (Chap. 100).

Because a majority of lung cancer patients present with advanced disease beyond the scope of surgical resection, there is understandable skepticism about the value of screening in this condition. Indeed, randomized controlled trials conducted in the 1960s to 1980s using screening chest x-rays (CXR), with or without sputum cytology, reported no impact on lung cancer–specific mortality in patients characterized as high risk (males age ≥45 years with a smoking history). These studies have been criticized for their design, statistical analyses, and outdated imaging modalities. The results of the more recently conducted Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) are consistent with these earlier reports. Initiated in 1993, participants in the PLCO lung cancer screening trial received annual CXR screening for 4 years, whereas participants in the usual care group received no interventions other than their customary medical care. The diagnostic follow-up of positive screening results was determined by participants and their physicians. The PLCO trial differed from previous lung cancer screening studies in that women and never smokers were eligible. The study was designed to detect a 10% reduction in lung cancer mortality in the interventional group. A total of 154,901 individuals between 55 and 74 years of age were enrolled (77,445 assigned to annual CXR screenings; 77,456 assigned to usual care). Participant demographics and tumor characteristics were well balanced between the two groups. Through 13 years of follow-up, cumulative lung cancer incidence rates (20.1 vs 19.2 per 10,000 person-years; rate ratio [RR], 1.05; 95% confidence interval [CI], 0.98–1.12) and lung cancer mortality (n = 1213 vs n = 1230) were identical between the two groups. The stage and histology of detected cancers in the two groups also were similar. These data corroborate previous recommendations *against* CXR screening for lung cancer.

In contrast to CXR, low-dose, noncontrast, thin-slice spiral chest computed tomography (LDCT) has emerged as an effective tool to screen for lung cancer. In nonrandomized studies conducted in the 1990s, LDCT scans were shown to detect more lung nodules and cancers than standard CXR in selected high-risk populations (e.g., age ≥60 years and a smoking history of ≥10 pack-years). Notably, up to 85% of the lung cancers discovered in these trials were classified as stage I disease and therefore considered potentially curable with surgical resection.

These data prompted the National Cancer Institute (NCI) to initiate the National Lung Screening Trial (NLST), a randomized study designed to determine if LDCT screening could reduce mortality from lung cancer in high-risk populations as compared with standard posterior anterior CXR. High-risk patients were defined as individuals between 55 and 74 years of age, with a ≥30 pack-year history of cigarette smoking; former smokers must have quit within the previous 15 years. Excluded from the trial were individuals with a previous lung cancer diagnosis, a history of hemoptysis, an unexplained weight loss of >15 lb in the preceding year, or a chest CT within 18 months of enrollment. A total of 53,454 persons were enrolled and randomized to annual screening yearly for three years (LDCT screening, n = 26,722; CXR screening, n = 26,732). Any noncalcified nodule measuring ≥4 mm in any diameter found on LDCT and CXR images with any noncalcified nodule or mass were classified as "positive." Participating radiologists had the option of not calling a final screen positive if a noncalcified nodule had been stable on the three screening exams. Overall, 39.1% of participants in the LDCT group and 16% in the CXR group had at least one positive screening result. Of those who screened positive, the false-positive rate was 96.4% in the LDCT group and 94.5% in the CXR group. This was consistent across all three rounds. In the LDCT group, 1060 cancers were identified compared with 941 cancers in the CXR group (645 vs 572 per 100,000 person-years; RR, 1.13; 95% CI, 1.03 to 1.23). Nearly twice as many early-stage IA cancers were detected in the LDCT group compared with the CXR group (40% vs 21%). The overall rates of lung cancer death were 247 and 309 deaths per 100,000 participants in the LDCT and CXR groups, respectively, representing a 20% reduction in lung cancer mortality in the LDCT-screened population (95% CI, 6.8–26.7%; $p = .004$). Compared with the CXR group, the rate of death in the LDCT group from *any* cause was reduced by 6.7% (95% CI, 1.2–13.6; $p = .02$) (Table 107-2). The