Shifting Paradigms in Non-Small Cell Lung Cancer: An Evolving Therapeutic Landscape

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Abstract

Globally, lung cancer is the leading cause of cancer-related mortality among both men and women, and while mortality associated with the disease has demonstrated relative stability over the years, evidence has suggested an increasing incidence and prevalence of the disease. Unfortunately, the diagnosis of lung cancer is often made late in the course of the disease, with almost 70% of patients presenting with locally advanced or metastatic disease at initial diagnosis. Non-small cell lung cancer (NSCLC) is the most common form of the malignancy, occurring in up to 85% of cases. There are 3 subtypes of NSCLC: squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma. Enhanced understanding of the pathophysiology of NSCLC has led to substantial improvements in diagnostic, prognostic, and therapeutic interventions for NSCLC. The discovery of targetable molecular alterations in genes, such as epidermal growth factor receptor (EGFR), has driven the evolution of targeted therapies for NSCLC and shifted treatment paradigms for the disease. This article will summarize the epidemiology and pathophysiology of NSCLC, its associated gene mutations and biomarkers, and the approach to treatment, with a focus on patients whose tumors harbor EGFR-activating mutations.

Am J Manag Care. 2013;19:S390-S397

For author information and disclosures, see end of text.

Lung cancer is the leading cause of cancer-related mortality in the world.[1] Unfortunately, the diagnosis is frequently made late in the course of lung cancer; nearly 70% of patients have locally advanced or metastatic disease at diagnosis. Among patients with lung cancer, 75% to 85% have non-small cell lung cancer (NSCLC), and 50% of those patients present with advanced metastatic disease (stage IV).[1,2] Recent research has led an to expansion of the diagnostic and treatment landscape beyond cytotoxic chemotherapy to include molecularly targeted therapies that inhibit key components of cellular pathways implicated in tumor growth and progression.[3] This article provides a clinical overview of NSCLC, its associated gene mutations, current targeted treatments, and predictive biomarkers, with particular focus on epidermal growth factor receptor (EGFR). The next article in the supplement explores recent recommendations on molecular profiling, the incorporation of molecular profiling into clinical practice, and the economic implications in a cost-constrained healthcare and managed care environment.

Epidemiology and Pathophysiology

Lung cancer, including both small-cell lung cancer and NSCLC, is the second most common cancer among men and women, and accounts for approximately 14% and 12% of all new cancer diagnoses in males and females, respectively. The American Cancer Society estimates that in 2013, there will be 228,190 new cases of lung cancer (118,080 in men; 110,110 in women) in the United States, with an estimated 159,480 deaths resulting from lung cancer (87,260 in men; 72,220 in women), accounting for roughly 27% of all cancer deaths.

Lung cancer is the leading cause of cancer-related death among both men and women, with more people dying from lung cancer than from colon, breast, and prostate cancers combined.[4] The estimated incidence of lung cancer has increased from 169,500 in 2001 to 228,190 in 2013; however, mortality appears to remain relatively stable (157,400 in 2001 to 159,480 in 2013), which suggests that the prevalence of the disease is also increasing.[1,4]

Due to the high mortality rate associated with lung cancer, it is important to identify risk factors associated with its development. Risk factors for lung cancer include: (1) current or former cigarette smoking; (2) proximity to cigarette smoking (ie, passive

inhalation); and (3) exposure to asbestos or radon. In men, the lifetime risk of developing lung cancer is about 1 in 13, and in women, the lifetime risk is about 1 in 16. When only smokers are considered, the risk is much higher, whereas the risk for nonsmokers is much lower.[4] When looking at the types of lung cancer, NSCLC is far more prevalent than small-cell carcinoma, accounting for 75% to 85% of lung cancer cases.[1,2]

Once lung cancer is present, one must examine the type, because it can affect treatment decisions. Lung cancer is characterized by histology and stage.[1,5] NSCLC consists of squamous-cell carcinoma (about 30% of all lung cancers), adenocarcinoma (about 30%-40% of all lung cancers), or large-cell carcinoma (about 10%-15% of all lung cancers). Small-cell carcinoma constitutes the remaining 20% to 25% and appears to have been decreasing in incidence over the last 30 years, possibly due to decreased cigarette smoking.[6] Small-cell lung cancer and squamous cell carcinoma are most strongly associated with smoking and are typically found in the central part of the chest. Adenocarcinomas are associated with smoking, but are also the most common lung cancer among nonsmokers and women. This subtype of NSCLC often grows near the periphery of the lung, and is more likely to metastasize to distant sites than squamous cell carcinoma. Similarly, large-cell carcinomas are also more likely to metastasize than squamous cell carcinoma. Small-cell carcinomas grow very rapidly, are very likely to be diagnosed in a metastatic state, and usually manifest centrally in the chest.[1] Staging of NSCLC is determined based upon the primary tumor, lymph node involvement, and the presence or absence of distant metastases.

In addition to the traditional risk factors that one might typically associate with lung cancer, age also plays a notable role in disease development and outcomes. Lung cancer predominantly develops in older individuals, with approximately 2 out of every 3 people diagnosed with lung cancer at 65 years or older.[4] Patients under the age of 45 years account for less than 2% of all cases of lung cancer. Factors that are associated with the diagnosis of lung cancer at a younger age include: (1) adenocarcinoma cancer type; (2) African American race; (3) Asian or Pacific Islander race; and (4) stage IV disease.[7] Overall, roughly 50% of patients with newly diagnosed NSCLC will have metastatic disease, and the 5-year survival following a diagnosis with NSCLC is less than 20%.[1,2] When compared with younger patients with the same stage of NSCLC, 5-year survival tends to be shorter among older patients.[7] In general, the prognosis of a patient with NSCLC is greatly affected by the stage at which the NSCLC is diagnosed (**Figure**).[8] Despite the very serious prognosis associated with lung cancer, much has been learned in recent years about the disease and the factors that impact treatment outcomes. Further, some individuals with earlier-stage cancers are able to be cured, including the 380,000 people who have been diagnosed with lung cancer at some point but are still alive today.[4]

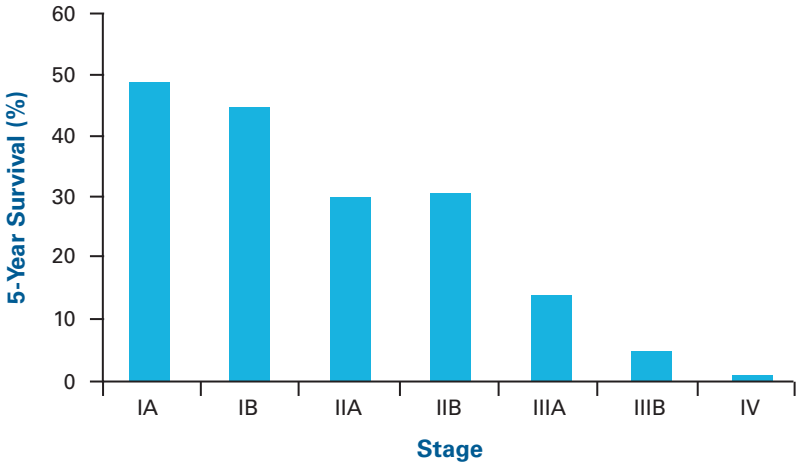
Targeted Therapies in NSCLC

There are several approaches to treating NSCLC, including surgical management for early stage and select locally advanced lung cancers, but for metastatic disease, systemic therapy is the mainstay of treatment.[1,2] Systemic therapy is available in 2 general categories, standard therapy and, more recently, targeted therapy. Systemic standard therapy consists of nonselective chemotherapy which targets the cell cycle of dividing cells. Targeted therapies were designed to selectively target molecular pathways that drive, or are responsible for, cancer cells in NSCLC. Because targeted therapies are more specific to the biology of the cancer cells than standard therapies, there is potential for reduced treatment-related toxicity.

To define the place in therapy of various targeted therapies, including the tyrosine kinase inhibitors (TKIs), this article includes a representative sampling of available literature rather than an exhaustive review of all treatment options. Multiple clinical trials have shown that chemotherapy in advanced NSCLC can reduce symptoms, improve survival, and benefit patient quality of life (QOL). The mainstay of front-line systemic therapy has been platinum-doublet chemotherapy with either cisplatin or carboplatin and a partner drug (typically gemcitabine, pemetrexed, vinorelbine, or a taxane such as docetaxel or paclitaxel). Despite these advances, NSCLC is still associated with a 5-year survival rate of 15%. [2]

One key factor associated with driving NSCLC is angiogenesis. Angiogenesis plays an important role in lung cancer growth and spread. Due to the role of angiogenesis in feeding NSCLC, the addition of the vascular endothelial growth factor inhibitor bevacizumab to a paclitaxel-carboplatin combination therapy versus paclitaxel-carboplatin alone was assessed for the possibility of enhanced efficacy.[9,10] In a phase 3 trial, the addition of bevacizumab to paclitaxel-carboplatin improved median survival in non-squamous NSCLC to 12.3 months versus 10.3 months with paclitaxel-carboplatin alone (hazard ratio [HR], 0.79; $P = .003$), with progression-free survival (PFS) of 6.2 months and 4.5 months (HR, 0.66; $P < .001$), respectively, and response rates of 35% and 15% ($P < .001$), respectively.[10] While the use of bevacizumab is associated with several adverse effects, including rash, diarrhea, headache, and minor bleeding episodes, bevacizumab is not used in squamous lung cancers

Figure. Rates of 5-Year Survival in NSCLC by Stage[8]



NSCLC indicates non-small cell lung cancer.
Adapted from American Cancer Society. Non small-cell cancer survival rates by stage. http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates. Accessed June 13, 2013.

because of the increased rate of pulmonary hemorrhage, which is sometimes fatal.

Pemetrexed is another therapy that is an inhibitor of thymidylate synthase and a general anti-folate inhibitor of purine and pyrimidine synthesis. The agent has been studied extensively as a chemotherapeutic agent in NSCLC.[11-13] Assessment of prognostic factors for efficacy of pemetrexed from phase 3 trials revealed enhanced efficacy in nonsquamous (ie, adenocarcinoma, large-cell carcinoma) histology relative to squamous histology. When compared with a cisplatin-gemcitabine combination therapy, cisplatin-pemetrexed demonstrated similar overall survival (10.3 months in both groups) in the overall population, which consisted of patients with stage IIIB or IV NSCLC and good performance status (Eastern Cooperative Oncology Group performance status of 0 to 1) using chemotherapy for the first time. However, in histologic subgroup analysis, improvements were noted in overall survival among the adenocarcinoma (10.9 months vs 12.6 months; $P = .03$) and large-cell carcinoma groups (6.7 months vs 10.4 months; $P = .03$), but not in the squamous cell group (10.8 months vs 9.4 months; $P = .05$).[12] The preferential efficacy of pemetrexed in non-squamous NSCLC may be attributed to higher levels of expression of thymidylate synthase and S-phase kinase-associated protein in squamous cell lung cancers than in non-squamous lung cancers.[13] Although pemetrexed was associated with lower rates of hematologic toxicity than gemcitabine, there were higher rates of nausea, dehydration, and fatigue in the premetrexed treatment group.[12]

Although the addition of bevacizumab and pemetrexed has improved patient outcomes, survival still remains poor, with overall survival approximately 10 to 12 months for patients with stage IIIB or IV disease. In addition, QOL is influenced by the quality of treatment and the patient's health status, and in recent QOL studies of second-line targeted therapies, quality-adjusted life-years scores ranged from 0.46 for progressive disease with grade 3/4 toxicity to 0.712 for responding disease without grade 3/4 toxicity.[14] The scale is based on a score of 0 for deceased to a score of 1 for perfect health, indicating that patients with NSCLC treated with these agents have 50% to 70% of a normal health status.[15,16] Patient QOL surveys have identified that the type of treatment and the adverse effects of treatment affected patient-perceived QOL, whereas gender, age, tumor stage, and survival time did not affect patient-perceived QOL.[17] Given the incurable nature of advanced NSCLC, future strategies are focused on the identification and targeting of patients with NSCLC tumors that express certain oncogenes that may respond to targeted therapies.

Molecular Aberrations in NSCLC

Paradigms for the treatment of metastatic NSCLC are shifting. A one-size-fits-all approach is no longer acceptable. The identification of molecular aberrations that predict individual responses to targeted therapeutics has altered the landscape of NSCLC therapy. The Lung Cancer Mutation Consortium, a collaboration of multiple academic medical centers (including Memorial Sloan-Kettering Cancer Center,

Dana-Farber Cancer Institute, MD Anderson Cancer Center, and Massachusetts General Hospital Cancer Center), conducted a molecular profiling of 1000 lung adenocarcinoma specimens and linked these results to clinical trials, as well as US Food and Drug Administration (FDA)-approved targeted agents. The consortium was able to identify potentially actionable mutations in over 60% of tumors from patients who had received treatment with FDA-approved targeted agents or those who had been enrolled in clinical trials. The most frequent and most important molecular changes include the V-Ki-ras2 Kirsten rat sarcoma oncogene homolog (KRAS) mutations (25%), EGFR mutations (23%), and anaplastic lymphoma kinase (ALK) translocations (6%).[18] The remaining sections will highlight what these mutations are and how they can be treated.

Focus on EGFR-Activating Mutations

The epidermal growth factor receptor (EGFR) gene family has long been recognized as a target to limit tumor growth and survival. It is part of a family of receptor tyrosine kinases, consisting of 4 genes that encode homologous receptors: (1) EGFR/ErbB1/HER1, (2) ErbB2/HER2/neu, (3) ErbB3/HER3, and (4) ErbB4/HER4.[19] The EGFR receptor contains an extracellular binding domain, a transmembrane lipophilic segment, and an intracellular protein tyrosine kinase domain. Particular EGFR mutations render it constitutively active, leading to downstream signaling activation, which causes cell proliferation, protection from apoptosis, and the development of metastases.[20-22]

Activating mutations in these EGFR-related genes at exons 18 to 21 can alter the course of the disease and treatment response to EGFR-TKIs in NSCLC.[3,23-26] The 2 most common mutations that activate EGFR are exon 19 deletions and a L858R point mutation on exon 21; these mutations account for approximately 90% of EGFR mutations.[27] EGFR-activating mutations occur more frequently among patients with adenocarcinoma histology, patients with a history of light smoking, women, East Asian populations, and patients who are nonsmokers.[24,28-30] The percentage of NSCLC patients with EGFR-activating mutations is roughly 10% in non-Asian populations and 40% among the Asian populations.[28] In a study published in 2009 by Mok et al, the selection of patients with advanced adenocarcinoma who were nonsmokers or former light smokers and were living in East Asia resulted in a study population in which 59.7% of patients had an EGFR mutation.[24]

In early clinical trials, the EGFR-TKI gefitinib was usually ineffective against NSCLC, but dramatic responses in a minority of patients eventually led to the identification of EGFR-activating mutations that predicted strong responses to EGFR-TKIs.[23] This discovery led to several clinical trials that explicitly selected patients with EGFR-activating mutations and treated them with EGFR-TKIs.

Multiple randomized phase 3 clinical trials have confirmed that EGFR-activating mutations do predict clinical benefit to EGFR-TKIs in NSCLC.[22,24-27,31-43] The Iressa Pan-Asia Study compared gefitinib with carboplatin-paclitaxel combination therapy in a patient population with advanced pulmonary adenocarcinoma selected for the presence of EGFR-activating mutations (ie, previously untreated East Asian nonsmokers or former light smokers) and found a 12-month PFS of 24.9% and 6.7% (P <.001), respectively.[24] In 261 patients whose tumors were positive for an EGFR-activating mutation, PFS was longer with gefitinib in comparison with carboplatin/paclitaxel (HR, 0.48; 95% confidence interval [CI] 0.36-0.64; P <.001); however, in the 176 patients lacking an EGFR mutation, PFS was significantly shorter among patients treated with gefitinib than with carboplatin-paclitaxel (HR, 2.85; 95% CI 2.05-3.98; P <.001).[24] In the multicenter, randomized, head-to-head phase 3 EURTAC study, which included a predominantly European study population, patients with advanced NSCLC and EGFR-activating mutations who were randomized to EGFR-TKI erlotinib treatment demonstrated significantly prolonged median PFS (9.7 vs 5.2 months; P <.0001) and higher response rates (58.1% vs 14.9%) compared with patients who were randomized to standard chemotherapy.[27] Several other randomized phase 3 clinical trials have also confirmed the high response rates and improvement in PFS of erlotinib and gefitinib when compared with standard chemotherapy as first-line treatment for metastatic NSCLC in patients whose tumors harbor EGFR-activating mutations.[33,40] It is important to note that patients who benefit the most from EGFR-TKIs must harbor the mutation in their tumor. A patient with the clinical characteristics of likely having an EGFR-activating mutation, but whose tumor tests negative for an EGFR mutation, may actually be harmed by initiating an EGFR-TKI as frontline treatment in lieu of chemotherapy.

Currently, there are several EGFR-TKIs that are approved for use in metastatic NSCLC in the United States—erlotinib, gefitinib, and afatinib—although their availability varies.[28,44-45] Erlotinib is approved as a first-line treatment for patients with metastatic lung cancer whose tumors harbor EGFR-activating mutations. It is also approved for all patients with metastatic NSCLC (not just those whose tumors harbor EGFR-activating mutations) in subsequent lines of therapy, as well as maintenance therapy in patients whose disease has not progressed after platinum doublet chemotherapy.[44] This

approval for use outside the scope of patients with EGFR-activating mutations is based on randomized clinical trials in patients with metastatic NSCLC who were not selected by EGFR mutations and demonstrated modest survival benefit compared with placebo as maintenance therapy and in subsequent lines of treatment after progression on first-line chemotherapy. In advanced NSCLC, patients who were not selected for EGFR mutations, had been previously treated with chemotherapy, and had received erlotinib 150 mg daily demonstrated an improved overall survival of 6.7 months versus 4.7 months with placebo (P = .001).[37] Patients receiving erlotinib as maintenance therapy after 4 cycles of platinum-doublet chemotherapy demonstrated a prolonged median overall survival of 12 months versus 11 months with placebo (P = .0088).[39]

In 2005, the FDA approved a modification of the labeling for gefitinib that limited its indication to use in patients who were currently benefiting or had previously benefited from gefitinib treatment in the opinion of their treating physician. Also, the use of gefitinib is supervised under the risk management program called the Iressa Access Program.[22,46] However, access is difficult because gefitinib is not available in the United States.

With regard to the availability of erlotinib, in July 2013, the distribution of erlotinib was changed, so that the medication would no longer be available to retail pharmacies, but supplied through select specialty pharmacies and authorized distributors to hospitals and physicians for in-house dispensing pharmacies.[47]

Afatinib is an irreversible EGFR inhibitor, whereas gefitinib and erlotinib bind reversibly to the ATP binding site of EGFR. Afatinib was recently approved by the FDA for the first-line treatment of metastatic NSCLC in patients with EGFR-activating mutations. Currently, there is no limited distribution program for afatinib, and it is readily available for use in the United States through authorized prescribers. The approval of afatinib was based on the LUX-Lung clinical trial program that showed significantly prolonged PFS in patients with EGFR-activating mutations who had received afatinib as frontline treatment in comparison with standard chemotherapy (11.1 vs 6.9 months; P = .0004).[48-52] Thus far, none of the phase 3 trials have shown an overall survival benefit when using EGFR-TKIs as first-line therapy instead of conventional chemotherapy. This is likely due to crossovers in clinical trials where patients in the chemotherapy control arm eventually received an EGFR-TKI in subsequent lines of therapy. However, it is worth noting that in Japan, the overall survival in patients with advanced lung adenocarcinoma and EGFR mutations prior to the approval of gefitinib ranged from 10.4 to 13.6 months, and increased to an average of 27.2 months following drug approval.[53]

It should be noted that the EGFR-TKIs are not without toxicity, and that the skin toxicity associated with those particular agents may be associated with improved response to the agents.[22] The most common adverse reactions experienced by patients taking EGFR-TKIs are diarrhea, rash/dermatitis acneiform rash, stomatitis, paronychia, dehydration, dry skin, decreased appetite, and pruritus. The most serious reactions are interstitial lung disease, bullous and exfoliative skin disorders, renal failure, hepatic failure, ulcerative keratitis, left ventricular dysfunction, and embryofetal toxicity.[28,44,45]

Resistance to EGFR-TKIs

A randomized study published in 2002 found that eligible patients with advanced NSCLC (N = 1155) who had received chemotherapy regimens of cisplatin plus paclitaxel, cisplatin plus gemcitabine, cisplatin plus docetaxel, or carboplatin plus paclitaxel demonstrated an overall 19% response rate to treatment, with a combined median survival and time to progression of disease of 7.9 months and 3.6 months, respectively.[54] The use of targeted EGFR-TKIs in patients with EGFR-activating mutations has been shown to increase median PFS to approximately 10 months, and these agents may improve outcomes for patients who are affected by a disease that is otherwise associated with a grim prognosis. Unfortunately, patients undergoing treatment with currently approved EGFR-TKIs will inevitably develop drug resistance; thus, it is important to identify alternative therapies that overcome acquired resistance to these agents.[55-60] The most common mutation for resistance (about 50%) is the secondary EGFR T790M mutation that prevents EGFR-TKIs from attaching to the ATP binding site on EGFR.[59] Increased EGFR copy number, EGFR bypass via alternative pathways such as MNNG HOS transforming gene (MET) amplification, phosphatidylinositol 3-kinase mutations, and HER2 amplification have all been described. The transformation from NSCLC to small cell histology has also been reported.[61,62] New drugs and therapeutic combinations are currently in clinical development in an effort to overcome EGFR-TKI resistance.

Other Emerging Treatment Strategies for Oncogene-Driven Subsets of NSCLC

A new era in lung cancer therapy has begun. Molecular aberrations that are able to predict positive responses to targeted agents have changed the landscape of treatment for metastatic NSCLC. Crizotinib is an agent that is now approved for the treatment of ALK+ NSCLC, based on

clinical trials that demonstrated high response rates in patients whose tumors harbored ALK translocations.[63] Proto-oncogene tyrosine-protein kinase ROS (ROS1) gene rearrangements share homology to ALK. Preclinical and early clinical data show high responsiveness of ROS1-rearranged lung cancers to crizotinib.[64] With the addition of newly discovered molecular aberrations such as HER2 mutations and RET (a receptor for members of the glial cell line-derived neurotrophic factor family) gene fusions, the full molecular heterogeneity of NSCLC is beginning to be discovered. These mutations predominantly occur in lung adenocarcinoma patients. However, mutations in squamous cell lung cancer that may also be targetable are now being identified. As identification of these molecular aberrations continue to expand, new agents and strategies will be developing at a rapid rate.[65-67]

The earliest identified and most frequently mutated of the group is KRAS. Unlike EGFR, ALK, and ROS1, some KRAS mutations are associated with a history of smoking, though other KRAS mutations are more frequently associated with patients without a significant smoking history. Currently, there are no FDA-approved therapies that specifically target KRAS-mutated NSCLC, but clinical trials of agents that are designed to inhibit MEK, a downstream protein activated by KRAS, have shown promise.

Crizotinib is an ALK and MET inhibitor that was recently approved by the FDA to treat ALK-rearranged NSCLC. In a phase 1 trial, high response rates (57%) were observed in patients with ALK-rearranged lung cancer.[68] This led to a phase 3 trial in patients with ALK-rearranged tumors that had progressed on front-line chemotherapy. Significantly increased response rates (65 vs 20%) and prolonged median PFS (7.7 vs 3 months, $P < .0001$) were observed when ALK+ patients receiving crizotinib were compared with patients who had received standard chemotherapy (docetaxel or pemetrexed).[69] The FDA approval did not specify line of cancer therapy; however, a clinical trial is currently evaluating crizotinib as first-line therapy in comparison with platinum-based agents and pemetrexed for patients with ALK-rearranged lung cancer.[66,67] ROS1 is a receptor tyrosine kinase that shares sequence homology with ALK, and patients with ROS1-rearranged lung cancer (about 2% of NSCLC tumors) have also demonstrated response to crizotinib. Clinical trials evaluating various ALK- and ROS1-TKIs in these types of patients are currently ongoing.[64]

Conclusion

Historically, metastatic NSCLC was associated with poor clinical outcomes. Efforts to recognize and target oncogene-driven subsets of NSCLC have identified molecular changes that are targetable with TKIs. This therapeutic milestone has dramatically improved patient outcomes in certain subsets of NSCLC—in particular, patients whose tumors harbor EGFR-activating mutations and ALK gene rearrangements. Efforts to identify other targetable molecular aberrations and to overcome the eventual development of resistance to TKIs are ongoing. In order to optimize treatment and tailor disease management to improve clinical outcomes, appropriate discriminative testing must be employed; this topic is discussed in detail in the next article in this supplement.

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Funding source: This activity is supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

Author disclosure: Dr Riess does not have any relevant financial relationships with commercial interests to disclose.

Authorship information: Concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and supervision.

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