Protocol

Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

(204143)

(Formerly Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer [Liquid Biopsy])

Medical Benefit		**Effective Date**: 04/01/19	**Next Review Date**: 01/20
Preauthorization	No	**Review Dates**: 01/18, 01/19	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced non-small-cell lung cancer	Interventions of interest are: • Testing for biomarkers of EGFR TKI sensitivity using circulating tumor DNA with the cobas EGFR Mutation Test v2	Comparators of interest are: • Testing for biomarkers of EGFR tyrosine kinase inhibitor sensitivity using tissue biopsy • No testing for biomarkers of EGFR tyrosine kinase inhibitor resistance	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity
Individuals: • With advanced non-small-cell lung cancer	Interventions of interest are: • Testing for biomarkers of EGFR TKI sensitivity using circulating tumor DNA with the Guardant360 or OncoBEAM tests	Comparators of interest are: • Testing for biomarkers of EGFR tyrosine kinase inhibitor sensitivity using tissue biopsy • No testing for biomarkers of EGFR tyrosine kinase inhibitor resistance	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity
Individuals: • With advanced non-small-cell lung cancer	Interventions of interest are: • Testing for biomarkers of EGFR TKI sensitivity using circulating tumor DNA with tests other than the cobas v2, Guardant360, or OncoBEAM	Comparators of interest are: • Testing for biomarkers of EGFR tyrosine kinase inhibitor sensitivity using tissue biopsy • No testing for biomarkers of EGFR tyrosine kinase inhibitor resistance	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity
Individuals: • With advanced non-small-cell lung cancer	Interventions of interest are: • Testing for biomarkers other than EGFR using liquid biopsy to select targeted therapy	Comparators of interest are: • Testing for biomarkers other than EGFR using tissue biopsy to select targeted therapy • No testing for biomarkers other than EGFR tyrosine	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity

Populations	Interventions	Comparators	Outcomes
		kinase inhibitor resistance	
Individuals: • With advanced non-small-cell lung cancer who progressed on EGFR tyrosine kinase inhibitors	Interventions of interest are: • Testing for biomarkers of EGFR tyrosine kinase inhibitor resistance using liquid biopsy	Comparators of interest are: • Testing for biomarkers of EGFR tyrosine kinase inhibitor resistance using tissue biopsy • No testing for biomarkers of EGFR tyrosine kinase inhibitor resistance	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity

DESCRIPTION

Genetic testing of circulating tumor DNA (ctDNA) and circulating tumor cells in peripheral blood (referred to as "liquid biopsy") potentially offers a noninvasive alternative to tissue biopsy for therapeutic decisions and prognosis in patients with cancer. For patients with non-small-cell lung cancer (NSCLC), detection of "driver mutations" or resistance variants is important for selecting patients for targeted therapy.

SUMMARY OF EVIDENCE

For individuals with advanced NSCLC who receive testing for biomarkers of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) sensitivity using ctDNA with the cobas EGFR Mutation Test v2 (liquid biopsy), the evidence includes numerous studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are overall survival, disease-specific survival, and test validity. Current evidence does not permit determining whether cobas or tissue biopsy is more strongly associated with patient outcomes or treatment response. No randomized controlled trials (RCTs) were identified providing evidence of the clinical utility of cobas. The cobas EGFR Mutation Test has adequate evidence of clinical validity for the EGFR TKI-sensitizing variants. The Food and Drug Administration has suggested that a strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the cobas test would result in an overall diagnostic performance equivalent to tissue biopsy. Several additional studies of the clinical validity of cobas have shown it to be moderately sensitive and highly specific compared with a reference standard of tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the cobas test should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with EGFR TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. The cobas test can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with advanced NSCLC who receive testing for biomarkers of EGFR TKI sensitivity using ctDNA (liquid biopsy) with the Guardant360 or OncoBEAM tests, the evidence includes several studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are overall survival, disease-specific survival, and test validity. Current evidence does not permit determining whether liquid or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of these tests. The Guardant360 and OncoBEAM tests have adequate evidence of clinical validity for the EGFR TKI-sensitizing variants. A strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the tests would result in an overall diagnostic performance similar to tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the Guardant360 or OncoBEAM tests should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds

of patients with EGFR TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with advanced NSCLC who receive testing for biomarkers of EGFR TKI sensitivity using ctDNA with tests other than the cobas EGFR Mutation Test v2, Guardant360, or OncoBEAM, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with tissue reference standard. Relevant outcomes are overall survival, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests other than the cobas, Guardant360, and OncoBEAM tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. Current evidence does not permit determining whether liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of those methods of liquid biopsy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with advanced NSCLC who receive testing for biomarkers other than EGFR using liquid biopsy to select a targeted therapy, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with the tissue biopsy reference standard. The relevant outcomes are overall survival, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision for variants other than EGFR. We found no RCTs providing evidence of the clinical utility of those of methods of liquid biopsy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with advanced NSCLC who progressed on EGFR TKIs who receive testing for biomarkers of EGFR TKI resistance using liquid biopsy, the evidence includes a few studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are overall survival, disease-specific survival, and test validity. For variants that indicate EGFR TKI resistance and suitability for alternative treatments with osimertinib, liquid biopsy is moderately sensitive and moderately specific compared with a reference standard of tissue biopsy. Given the moderate clinical sensitivity and specificity of liquid biopsy, using liquid biopsy alone or in combination with tissue biopsy might result in the selection of different patients testing positive for EGFR TKI resistance. It cannot be determined whether patient outcomes are improved. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

EGFR TESTING

Except as noted below, analysis of two types of somatic sensitizing variants within the epidermal growth factor receptor (EGFR) gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—using the cobas® EGFR Mutation Test v2, Guardant360 test, or OncoBEAM test with plasma specimens to detect circulating tumor DNA (ctDNA) may be considered **medically necessary** as an alternative to tissue biopsy to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy in patients with advanced stage III or IV non-small-cell lung cancer (NSCLC). The cobas® test is a companion diagnostic for erlotinib and gefitinib.

Analysis of other EGFR-sensitizing variants within exons 18 to 24 using ctDNA for applications related to NSCLC is considered **investigational**.

Analysis of the EGFR T790M resistance variant for targeted therapy with osimertinib using ctDNA or for other applications related to NSCLC, is considered **investigational**.

Analysis of two types of somatic variants within the EGFR gene—small deletions in exon 19 and a point variant in exon 21 (L858R)—using ctDNA is considered **investigational** for patients with advanced NSCLC of squamous cell type.

ALK TESTING

Analysis of somatic rearrangement variants of the ALK gene using plasma specimens to detect ctDNA or RNA is considered **investigational** as an alternative to tissue biopsy to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with NSCLC.

BRAF V600E TESTING

Analysis of the BRAF V600E variant using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar], trametinib [Mekinist]) in patients with NSCLC.

ROS1 TESTING

Analysis of somatic rearrangement variants of the ROS1 gene using plasma specimens to detect ctDNA or RNA is considered **investigational** as an alternative to tissue biopsy to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients NSCLC.

KRAS TESTING

Analysis of somatic variants of the KRAS gene using plasma specimens to detect ctDNA is considered **investigational** as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC.

OTHER GENES

Analysis of alterations in the HER2, RET, and MET genes using plasma specimens to detect ctDNA for targeted therapy in patients with NSCLC is considered **investigational**.

POLICY GUIDELINES

The tests discussed herein are intended for use in patients with advanced (stage III or IV) NSCLC Patients with sensitizing variants of the tyrosine kinase domain of the EGFR gene are considered good candidates for treatment with erlotinib, gefitinib, afatinib, or osimertinib. The Food and Drug Administration (FDA) approval for the cobas® EGFR Mutation Test v2 states that patients who are negative for EGFR exon 19 deletions or L858R variant based on the plasma test should be reflexed to routine biopsy and testing using formalin-fixed paraffin-embedded tissue. However, the plasma test may also be appropriate for patients who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, cannot undergo biopsy or have indeterminate histology (in whom an adenocarcinoma component cannot be excluded).

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing protocol

review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

BACKGROUND

PREDICTIVE BIOMARKERS IN NON-SMALL-CELL LUNG CANCER

Several predictive genetic biomarkers have been identified for non-small-cell lung cancer (NSCLC). Somatic genome alterations known as "driver mutations" are usually transformative variants arising in cancer cells in genes encoding for proteins important in cell growth and survival. RCTs have demonstrated improved efficacy, often in conjunction with decreased toxicity, of matching targeted therapies to patients with specific driver mutations. Several such targeted therapies are approved by the Food and Drug Administration (FDA) for NSCLC. Guidelines generally suggest analysis of either the primary NSCLC tumor or of a metastasis for the presence of a set of driver mutations to select appropriate treatment.

Genetic Biomarkers With FDA-Approved Targeted Therapies

The list of targeted therapies approved for NSCLC is evolving. Currently, there are FDA-approved targeted therapies for EGFR variants, anaplastic lymphoma kinase (ALK) translocations, ROS1 translocations, and BRAF variants for NSCLC. Companion diagnostics using tissue samples have also been FDA-approved to identify the associated driver mutations for the targeted therapies. The evaluation of molecular analysis of tissue samples for targeted therapy of NSCLC is found in the Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer Protocol.

EGFR Variants

Specific EGFR variants confer sensitivity to treatment with TKIs, such as erlotinib, gefitinib, afatinib, and osimertinib; the most common variants are deletions in exons 19 and an exon 21 substitution variant (L858R). These variants are referred to as TKI-sensitizing variants and are found in approximately 10% of white patients and up to 50% of Asian patients. The prevalence of EGFR variants is not well characterized in other ethnic or racial

groups but is estimated to be 10% to 15% in studies including general U.S. populations. TKIs are indicated as first-line treatment for patients with sensitizing variants; progression-free survival is improved with the use of TKIs. Patients receiving TKIs have fewer treatment-related adverse events than patients receiving cytotoxic chemotherapy.

ALK and ROS1 Translocations

ALK rearrangements confer resistance to TKIs. Approximately 4% of patients have ALK rearrangements. The TKI crizotinib, an inhibitor of ALK, ROS1, and mesenchymal-epithelial transition (MET) tyrosine kinases, is indicated in patients with ALK-positive tumors. In randomized trials comparing crizotinib with standard chemotherapy in ALK-positive patients, crizotinib has been associated with improved progression-free survival, response rates, lung cancer symptoms, and quality of life. ROS1 rearrangements develop in 1% to 2% of patients. For such patients, crizotinib has been shown to be effective, with response rates of about 70%.

BRAF Variants

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the BRAF gene is the most frequently mutated in NSCLC, in 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. BRAF or MEK inhibition with TKIs (e.g., vemurafenib/dabrafenib or trametinib) was originally approved by FDA for treatment of unresectable or metastatic melanoma with BRAF V600 variants but the combination of dabrafenib and trametinib was expanded to include treatment of metastatic NSCLC in 2017.

Genetic Biomarkers With Off-Label Targeted Therapies

Proposed targeted therapies may be used off-label for genetic alterations in HER2 (trastuzumab, afatinib), MET (crizotinib), and RET (cabozantinib). Human epidermal growth factor receptor 2 (HER2) is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. HER2 is expressed in approximately 25% of NSCLC. RET (rearranged during transfection) is a proto-oncogene that encodes a receptor tyrosine kinase growth factor. RET fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas. MET amplification is one of the critical events for acquired resistance in EGFR-mutated adenocarcinomas refractory to EGFR TKIs. MET amplification occurs in 2% to 4% of treatment-naive NSCLC and MET and EGFR comutations occur in 5% to 20% of NSCLC tumors with acquired resistance to EGFR TKIs.

Genetic Biomarkers Without Targeted Therapies

The most common predictive variant in North American populations is KRAS, occurring in 20% to 25% of NSCLC. Patients with KRAS variants have shorter survival than those without KRAS variants, and thus KRAS is a prognostic marker. It also predicts a lack of TKI efficacy. Because KRAS variants are generally not found with other tumor biomarkers, KRAS testing might identify patients who would not benefit from further molecular testing. Targeted therapies are under investigation for KRAS-variant NSCLC.

Tyrosine Kinase Inhibitor-Resistance Variants

EGFR Variants

The EGFR variant T790M has been associated with acquired resistance to TKI therapy. When the T790M variant is detected in tissue biopsies from patients with suspected resistance to TKI therapy, osimertinib is recommended as second-line therapy. However, the use of osimertinib as a first-line therapy for patients who have EGFR-sensitizing variants is emerging and may prevent the development of T790M resistance.

TREATMENT SELECTION

Tissue Biopsy as a Reference Standard

The standard for treatment selection in NSCLC is biomarker analysis of tissue samples obtained by biopsy or surgery. However, a lung biopsy is invasive with a slow turnaround time for obtaining results. Tissue biopsy may also be an imperfect reference standard due to inadequate sampling, tumor heterogeneity, or other factors.

Technologies for Detecting Circulating Tumor DNA

Cell-free DNA in blood is derived from nonmalignant and malignant cell DNA. The small DNA fragments released into the blood by tumor cells are referred to as circulating tumor DNA (ctDNA). Most ctDNA is derived from apoptotic and necrotic cells, either from the primary tumor, metastases or circulating tumor cells.[1] Unlike apoptosis, necrosis is considered a pathologic process, generating larger DNA fragments due to an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origins. The ctDNA can be used for genomic characterization of the tumor and identification of the biomarkers of interest.

Detection of ctDNA is challenging because cell-free DNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cell-free DNA. Therefore, methods up to 500 to 1000 times more sensitive than standard sequencing approaches (e.g., Sanger) are needed.

Sensitive and specific methods are available to detect ctDNA and identify single nucleotide variants, duplications, insertions, deletions, and structural variants. Examples of methods are as follows:

- Denaturing high-performance liquid chromatography involves polymerase chain reaction (PCR) followed by denaturing plus hybridization and then separation.
- Peptide nucleic acid-locked nucleic acid PCR suppresses wild-type EGFR followed by enrichment for mutated EGFR.
- Amplification refractory mutation system PCR generates different-sized PCR products based on the allele followed by separation of PCR fragments to determine the presence of variants.
- BEAMing combines emulsion PCR with magnetic beads and flow cytometry.
- Digital genomic technologies, such as droplet digital PCR, allow for enumeration of rare variants in complex mixtures of DNA.

Genetic testing of ctDNA can be targeted at specific genes or at commonly found, acquired, somatic variants ("hotspots") that occur in specific cancers, which can impact therapy decisions (e.g., EGFR and ALK in NSCLC); such testing can also be untargeted and may include array comparative genomic hybridization, next-generation sequencing (NGS), and whole exome and genome sequencing. Panel testing for specific genetic variants that may impact therapy decisions in many different cancers can also be performed.

REGULATORY STATUS

In June 2016, cobas® EGFR Mutation Test v2 (Roche Molecular Systems), a real-time PCR test, was approved by FDA through the premarket approval process (P150047).[2] This plasma test is a real-time PCR test approved as a companion diagnostic aid for selecting NSCLC patients who have EGFR exon 19 deletions, and L858R substitution variants, for treatment with erlotinib. A premarket approval supplement expanded the indication to include the test as a companion diagnostic for treatment with gefitinib in 2018 (P120019). Patients who test negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for EGFR variants. A previously approved version two of this test, which used tissue biopsy specimens, was also approved for detec-

tion of T790M variants in tissue, which are used to select patients to receive osimertinib. Approval of version two of the plasma test did not include detection of T790M variants.

No other ctDNA tests have FDA approval. However, Foundation Medicine was granted FDA breakthrough device designation for FoundationACT™ in 2018.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Several companies market tests that detect tumor markers from peripheral blood, including TKI-sensitizing variants for NSCLC. Laboratories that offer LDTs must be licensed by the Clinical Laboratory Improvement Amendments CLIA for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test. Clinical laboratories accredited through the College of American Pathologists enroll in proficiency testing programs to measure the accuracy of the test results. There are currently no College of American Pathologists proficiency testing programs available for ctDNA testing to ensure the accuracy of ctDNA LDTs.

Foundation Medicine's FoundationACT™ uses hybrid capture-based NGS to detect variants in over 60 genes for targeted therapy in metastatic cancer.

Guardant Health markets the Guardant360® test. This test uses NGS to identify variants in 73 genes associated with several different cancers.

Circulogene Theranostics' liquid biopsy test uses a finger stick blood sample and NGS to monitor known tumor variants (≈3000) in 50 cancer-associated genes for targeted therapy. The test uses a proprietary method to recover necrotic and apoptotic cell death-associated cell-free DNA.

Biocept offers blood-based assays that target variants found in lung and breast cancers. The test uses a proprietary real-time quantitative PCR and, using Sanger sequencing, sequences the amplified product to confirm variants.

Biodesix's GeneStrat® uses droplet digital PCR to analyze cell-free DNA and RNA to identify specific driver variants for which targeted therapy is available for NSCLC.

Resolution Bio offers ctDx-Lung™ uses NGS to detect single nucleotide variants, insertions and deletions, fusions, and copy number variants in approximately 20 genes targeted by a specific FDA-approved therapy or therapies in clinical trials.

Sysmex OncoBEAM™ offers liquid biopsies using BEAMing technology to detect variants in EGFR, KRAS, and BRAF for NSCLC as well as liquid biopsies for breast, melanoma, and colorectal cancer.

RELATED PROTOCOLS

Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Miscellaneous Genetic and Molecular Diagnostic Tests

Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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