Supplemental online content for:


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eTable 1: Variables Coded for Private and Medicare Policies
eAppendix 1: Definitions
eAppendix 2: Canary Insights Database
eAppendix 3: Policy Search Validation
eAppendix 4: Description of ctDNA Tests Used in Any ctDNA Panel
<table>
<thead>
<tr>
<th>Variable name</th>
<th>Variable Definition</th>
<th>Variable Details/Coding</th>
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</thead>
<tbody>
<tr>
<td>Policy unique ID</td>
<td>Automatic unique number</td>
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</tr>
<tr>
<td>Payer name</td>
<td>Payer full name</td>
<td>(eg, Aetna)</td>
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<tr>
<td>Policy name</td>
<td>Official name of policy</td>
<td>(Copy from Policy Source Information Table)</td>
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<tr>
<td>Policy type</td>
<td>Type of policy focus</td>
<td>Genetic testing overall</td>
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<tr>
<td></td>
<td></td>
<td>Tumor markers overall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expanded molecular testing panel overall</td>
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<tr>
<td></td>
<td></td>
<td>Liquid biopsy overall (ctDNA and circulating tumor cells)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ctDNA NCSLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ctDNA solid tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third-party policy (eg, AIM, eviCore)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test-specific (eg, Guardant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Policy from third party?</td>
<td>Was this policy adapted by the payer from a third party (eg, eviCore)?</td>
<td>Yes (note third party)/No</td>
</tr>
<tr>
<td>Most recent policy date</td>
<td>Date of policy</td>
<td>(MM/DD/YYYY)</td>
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<tr>
<td>Policy identified in search</td>
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<td>Yes/No</td>
</tr>
<tr>
<td>Coverage</td>
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<td>Yes/No</td>
</tr>
<tr>
<td>How coverage worded</td>
<td>What is covered in summary (cancer type, genes, test)</td>
<td>Summarize from copy/paste</td>
</tr>
<tr>
<td>Cancers included</td>
<td>Covered cancers (eg, lung cancer, pan-cancer, solid tumors)</td>
<td>Copy/Paste from policy</td>
</tr>
<tr>
<td>Test covered for monitoring</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>How is monitoring covered?</td>
<td>Short description if applicable</td>
<td>Copy/Paste or summarize</td>
</tr>
<tr>
<td>What ctDNA testing is covered</td>
<td>Names of tests covered, if specified, or “general ctDNA or multigene tests”</td>
<td>Copy/Paste from policy</td>
</tr>
<tr>
<td>Not covered language</td>
<td>Words used to describe what is not covered</td>
<td>Copy/Paste from policy</td>
</tr>
<tr>
<td>Covered clinical scenario</td>
<td>For which clinical indications is next-generation tumor sequencing considered medically necessary (eg, all solid tumors, advanced lung cancer, hematologic cancers)</td>
<td>Copy/Paste from policy</td>
</tr>
</tbody>
</table>
eAppendix 1. Definitions

**Cell-Free DNA (cfDNA)** are degraded DNA fragments released to the blood plasma. cfDNA can be used to describe various forms of DNA freely circulating the bloodstream, including circulating tumor DNA (ctDNA) and cell-free fetal DNA (cffDNA). Elevated levels of cfDNA are observed in cancer, especially in advanced disease.

**Circulating Tumor DNA (ctDNA)** is tumor-derived fragmented DNA in the bloodstream that is not associated with cells. ctDNA should not be confused with cell-free DNA (cfDNA), a broader term which describes DNA that is freely circulating in the bloodstream, but is not necessarily of tumor origin. ctDNA originates directly from the tumor or from circulating tumor cells (CTCs). Because ctDNA may reflect the entire tumor genome, it has gained traction for its potential clinical utility; “liquid biopsies” in the form of blood draws may be taken at various time points to monitor tumor progression throughout the treatment regimen.

**Circulating Tumor Cells (CTCs)** are whole tumor cells shed into the vasculature from a primary tumor and are carried around the body in the blood. CTCs may constitute seeds for subsequent growth of additional tumors (metastasis) in distant organs, a mechanism that is responsible for most cancer-related deaths. We do not examine coverage policies for CTC testing in this study.

**Liquid Biopsy** is a term used to refer to the analysis of ctDNA or CTCs from blood, urine, or other fluid.

eAppendix 2. Canary Insights Database

The Canary Insights Database (http://canaryinsights.com/) is a medical policy library containing >40,000 medical policies from commercial payers and links to public payer policies. Canary Insights continuously mines coverage and reimbursement changes for therapy and products. Canary Insights performs a daily search using a proprietary search engine on >200 payers and related healthcare sites, including Medicare, Medicaid, and hundreds of commercial insurance companies, and is updated on a daily basis. It does not include actual public payer coverage policies but does link to the Centers for Medicare & Medicaid Services website. Canary Insights provides a search engine that allows one to use keywords and select payers to identify private payer policies. The most current version of the policy is accessible via a link to the actual payer website, and past versions are provided in a PDF format. Individual Policy Data are validated as a direct product from the payer’s website (via a link or a PDF of the previous policy) and not abstracted/curated by Canary Insights (ie, data were not abstracted by Canary Insights).

eAppendix 3. Policy Search Validation

We used an iterative approach to identifying the best keywords to identify ctDNA-based panel tests. Specifically, we used a previous sample of 2015–2018 ctDNA policies and noted their titles. We found that nearly all included the terms “liquid biopsy” or “circulating tumor DNA.” We also found that some policies were written with general terminology in their titles, such as “expanded cancer panels” or “noncovered services.” We validated our terms by confirming that we did not find any instances of ctDNA-based coverage determinations within other policies (eg, Hereditary Cancer Genetic Testing) or that the policies we did identify (and subsequently included) using our search terms did not refer to additional policies that may include a ctDNA-based panel test coverage determination. For example, in all policies that referred to additional policies, we verified that they referred to policies that did not contain further information or determinations on ctDNA-based panel test coverage.

eAppendix 4. Description of ctDNA Tests Used in Any ctDNA Panel

NOTE: Tests that were named in any circulating tumor DNA (ctDNA)–based panel test coverage policy are described below. Inclusion of a named test that interrogates a single gene below should not construe coverage policies for single gene tests were included in this study.

**cobas EGFR Mutation Test v2**
Manufacturer: Roche
Cancer Type: Non–small cell lung cancer (NSCLC)
Test Sample: Cell-free DNA (cfDNA)
FDA Approval: Yes
Number of Genes Analyzed: 1 (EGFR)
Test Purpose (per manufacturer):
The cobas EGFR Mutation Test v2 is a real-time PCR test for the qualitative detection of defined mutations of the \textit{EGFR} gene in patients with NSCLC. Defined \textit{EGFR} mutations are detected using DNA isolated from formalin-fixed paraffin-embedded tumor tissue or cfDNA from plasma derived from EDTA anticoagulated peripheral whole blood.

The test is intended to aid in identifying patients with NSCLC whose tumors have defined \textit{EGFR} mutations and for whom safety and efficacy of a drug have been established as follows: Tarceva (erlotinib), exon 19 deletions and L858R; Tagrisso (osimertinib), T790M. Drug safety and efficacy have not been established for the following \textit{EGFR} mutations also detected by the cobas EGFR Mutation Test v2: Tarceva (erlotinib), G719X, exon 20 insertions, T790M, S768I, and L861Q; Tagrisso (osimertinib), G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q.

\textbf{Guardant360}

- Manufacturer: Guardant Health
- Cancer Type: NSCLC, pan-cancer
- Test Sample: ctDNA
- FDA Approval: No
- Number of Genes Analyzed: 73 genes, 23 indels, 18 amplifications, 6 fusions
- Test Purpose (per manufacturer):
  - Guardant360 is a laboratory test, which is performed with a blood sample. Patients are suitable for this test if they have a solid tumor in an advanced stage (stage III or IV) and are planned to be treated with targeted drugs.
  - Before first-line treatment: Get ahead of the challenges of tissue testing in advanced NSCLC by utilizing Guardant360 to guide first-line treatment decisions
  - At progression: Obtain genomic information on >70 genes relevant across multiple solid tumors including MSI-high to help find pan cancer therapies and clinical trials. Furthermore, in case of progression or when there is a tumor that is not responding to therapy after some time, it can be examined if probably further mutations came along, which are relevant for therapy planning. It can happen during a cancer therapy that a tumor develops strategies, so-called resistance mechanisms, via further mutations to avoid therapy and continue to spread.
  - Monitoring and aftercare: Guardant360 can be applied for the monitoring and aftercare of a cancer therapy as well. The liquid biopsy can be used to not only detect present mutations but also determine the level of present ctDNA in general. Therefore, whether a tumor responds to a corresponding therapy with targeted drugs, chemotherapeutics, or any other cancer therapy it be periodically observed without a big intervention. When a high level of tumor cells is present in the body, there is also a higher level of ctDNA in the blood. If a tumor responds to a therapy and decreases, the level of ctDNA in the blood also decreases or disappears.

\textbf{InVisionFirst-Lung}

- Manufacturer: Inivata
- Cancer Type: NSCLC
- Test Sample: ctDNA
- FDA Approval: No
- Number of Genes Analyzed: 36
- Test Purpose (per manufacturer):
  - InVisionFirst-Lung is a qualitative laboratory-developed test that uses targeted advanced sequencing technology to detect single nucleotide variants, copy number variants, insertions and deletions (indels), and structural variants in selected genes from DNA isolated from plasma samples from patients with NSCLC. The test is intended to aid clinicians in making treatment decisions for patients with NSCLC.

\textbf{OncoBEAM for Lung Cancer-1}

- Manufacturer: Sysmex Inostics
- Cancer Type: NSCLC
- Test Sample: ctDNA
- FDA Approval: No
- Number of Genes Analyzed: 1 (\textit{EGFR})
- Test Purpose (per manufacturer):
  - The highly sensitive BEAMing technology, a liquid biopsy with OncoBEAM, requires only a simple blood draw to access tumor DNA and provide a real-time view of a tumor's mutation status.
  - The test analyzes the \textit{EGFR} sensitizing mutations del19, L858R, and L861Q, and resistant mutations T790M, C797S.
  - NSCLC tumors with sensitizing \textit{EGFR} mutations have increased sensitivity to tyrosine kinase inhibitors (TKIs). Patients who initially respond to TKI therapy frequently relapse, with 60% of those on TKIs developing resistance due to the \textit{EGFR} T790M mutation.
OncoBEAM EGFR can identify the T790M mutation in patients whose disease has progressed on first-line TKI therapy, delivering rapid results and avoiding the need for a repeat tissue biopsy.

**OncoBEAM for Lung Cancer-2**  
Manufacturer: Sysmex Inostics  
Cancer Type: NSCLC  
Test Sample: ctDNA  
FDA Approval: No  
Number of Genes Analyzed: 3 (EGFR, KRAS, BRAF)  
Test Purpose (per manufacturer):  
1. The highly sensitive BEAMing technology, a liquid biopsy with OncoBEAM, requires only a simple blood draw to access tumor DNA and provide a real-time view of a tumor’s mutation status.  
2. The test analyzes the EGFR sensitizing mutations del19, L858R, and L861Q, and resistant mutations T790M, C797S; KRAS codons 12, 13, and 61; and BRAF V600E.  
3. NSCLC tumors with sensitizing EGFR mutations have increased sensitivity to TKIs. Patients who initially respond to TKI therapy frequently experience relapse, with 60% of those on TKIs developing resistance due to the EGFR T790M mutation.  
4. OncoBEAM EGFR can identify the T790M mutation in patients who have experienced disease progression on first-line TKI therapy, delivering rapid results and avoiding the need for a repeat tissue biopsy.  
5. OncoBEAM KRAS can identify multiple KRAS mutations, providing a more complete picture of a patient’s condition to rapidly inform critical therapy decisions. KRAS mutations occur in 25% of NSCLC cases. Independent of therapy, KRAS mutations can indicate poor survival rates compared with tumors without KRAS mutations.  
6. OncoBEAM BRAF tests for the BRAF V600E mutation, helping doctors to decide whether to initiate first-line therapy as soon as possible. BRAF mutations are detected in approximately 3% of patients with NSCLC. In 2017, the NCCN Clinical Practice Guidelines in Oncology for NSCLC were updated to include BRAF V600E mutation testing for all newly diagnosed patients to inform appropriate administration of first-line therapy, which now includes BRAF-targeted therapies.

**References**  