Local Coverage Determination (LCD): MolDX: Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer (L37897)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Contractor Information

<table>
<thead>
<tr>
<th>CONTRACTOR NAME</th>
<th>CONTRACT TYPE</th>
<th>CONTRACT NUMBER</th>
<th>JURISDICTION</th>
<th>STATE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noridian Healthcare Solutions, LLC</td>
<td>A and B MAC</td>
<td>01111 - MAC A</td>
<td>J - E</td>
<td>California - Entire State</td>
</tr>
<tr>
<td>Noridian Healthcare Solutions, LLC</td>
<td>A and B MAC</td>
<td>01112 - MAC B</td>
<td>J - E</td>
<td>California - Northern</td>
</tr>
<tr>
<td>Noridian Healthcare Solutions, LLC</td>
<td>A and B MAC</td>
<td>01182 - MAC B</td>
<td>J - E</td>
<td>California - Southern</td>
</tr>
</tbody>
</table>
| Noridian Healthcare Solutions, LLC| A and B MAC  | 01211 - MAC A  | J - E        | American Samoa
Guam
Hawaii
Northern Mariana Islands |
| Noridian Healthcare Solutions, LLC| A and B MAC  | 01212 - MAC B  | J - E        | American Samoa
Guam
Hawaii
Northern Mariana Islands |
| Noridian Healthcare Solutions, LLC| A and B MAC  | 01311 - MAC A  | J - E        | Nevada                            |
| Noridian Healthcare Solutions, LLC| A and B MAC  | 01312 - MAC B  | J - E        | Nevada                            |
| Noridian Healthcare Solutions, LLC| A and B MAC  | 01911 - MAC A  | J - E        | American Samoa
California - Entire State
Guam
Hawaii
Nevada
Northern Mariana Islands |

LCD Information

Document Information

Created on 02/06/2020. Page 1 of 15
LCD ID
L37897

LCD Title
MolDX: Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer

Proposed LCD in Comment Period
N/A

Source Proposed LCD
DL37897

AMA CPT / ADA CDT / AHA NUBC Copyright Statement
CPT codes, descriptions and other data only are copyright 2019 American Medical Association. All Rights Reserved. Applicable FARS/HHSARS apply.

Current Dental Terminology © 2019 American Dental Association. All rights reserved.

Copyright © 2019, the American Hospital Association, Chicago, Illinois. Reproduced with permission. No portion of the AHA copyrighted materials contained within this publication may be copied without the express written consent of the AHA. AHA copyrighted materials including the UB-04 codes and descriptions may not be removed, copied, or utilized within any software, product, service, solution or derivative work without the written consent of the AHA. If an entity wishes to utilize any AHA materials, please contact the AHA at 312-893-6816. Making copies or utilizing the content of the UB-04 Manual, including the codes and/or descriptions, for internal purposes, resale and/or to be used in any product or publication; creating any modified or derivative work of the UB-04 Manual and/or codes and descriptions; and/or making any commercial use of UB-04 Manual or any portion thereof, including the codes and/or descriptions, is only authorized with an express license from the American Hospital Association. To license the electronic data file of UB-04 Data Specifications, contact Tim Carlson at (312) 893-6816 or Laryssa Marshall at (312) 893-6814. You may also contact us at ub04@healthforum.com.

CMS National Coverage Policy
Created on 02/06/2020. Page 2 of 15
Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that “are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.”

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

**Coverage Guidance**

**Coverage Indications, Limitations, and/or Medical Necessity**

This test is a “liquid biopsy.” It is intended to assist physicians caring for patients who suffer from a common form of lung cancer and who have advanced disease.

This policy provides limited coverage for InVisionFirst™ - Lung (Inivata, Research Triangle Park, NC) (hereafter InVision) a plasma-based, somatic comprehensive genomic profiling test (CGP) for patients with advanced (Stage IIIIB/IV) non-small cell lung cancer (NSCLC):

- **At diagnosis and untreated**
  - When results for EGFR single nucleotide variants (SNVs) and insertions and deletions (indels); rearrangements in ALK and ROS1; and SNVs for BRAF are not available **AND**
  - When tissue-based CGP is infeasible [i.e., quantity not sufficient (QNS) for tissue-based CGP or invasive biopsy is medically contraindicated],

  or

- **At progression**
  - For patients progressing on or after chemotherapy or immunotherapy who have not been tested for EGFR SNVs and indels; rearrangements in ALK and ROS1; and SNVs for BRAF, and for whom tissue-based CGP is infeasible;
  - For patients progressing on EGFR tyrosine kinase inhibitors (TKIs).

If no genetic alteration is detected by InVision or if circulating tumor DNA (ctDNA) is insufficient/not detected, tissue-based genotyping should be considered.

**Summary of Evidence**

**Background**

It is estimated that more than 222,500 new cases of lung cancer will be diagnosed in the United States (US) this year.¹ This represents roughly 13% of all new cancer diagnoses and 26% of cancer deaths.¹ At least 87% of lung cancer is NSCLC.² The estimated 5-year survival rate for all NSCLC cancer patients is 17%, and only 4% for patients with advanced (stage IIIIB/IV) disease.³

The pathophysiological development of lung cancer is complicated, with several known genomic alterations found individually or in combination in many patients. These alterations may be due to toxic exposure or underlying genetic
factors, and not all alterations have the same impact on disease development or prognosis. Some alterations appear to be integral to the transformation and ongoing growth of the tumor (driver alterations).

Among the best-studied genomic alterations are EGFR single nucleotide variants (SNVs) and insertions/deletions (indels) and EML4-ALK rearrangements/fusions. EGFR-mutated NSCLC comprises up to 15% of all NSCLC patients in the US, with higher prevalence in certain ethnic groups (e.g., 40% in Asian Americans and 26% in Latin Americans). These mutations convey a more favorable prognosis and predict response to treatment with oral EGFR inhibitors such as erlotinib, gefitinib, osimertinib or afatinib. Rearrangements of ALK and EML4, or with other less common fusion partners, occur in approximately 4% of all NSCLC patients and predict response to treatment with oral ALK-targeted inhibitors such as crizotinib, ceritinib, or alectinib. Recently, dabrafenib in combination with trametinib has been approved for BRAF V600E positive metastatic NSCLC.

Genomic alterations in NSCLC vary by smoking history, ethnicity and age. Sequencing of tumor specimens in never-smokers demonstrates a higher mutation prevalence of EGFR than in smokers. Some non-smoking ethnic groups, such as Asian women, have a much higher mutation prevalence than their Caucasian counterparts. Prevalence of ALK rearrangements is also higher in non-smokers. In contrast, smokers have a higher prevalence of targetable alterations in the MET and BRAF genes.

**Tumor Tissue Genotyping**

Failure of oncologists to order genotyping, inadequate quantity or quality of tissue specimen, and the necessity for repeat invasive biopsies with their associated complications and costs are just a few issues that confound tumor-tissue genotyping. Traditionally, tumor genotyping has been conducted by direct interrogation of tumor tissue obtained through invasive tissue sampling procedures. However, this diagnostic approach is limited by the availability of sufficient tumor tissue and the ability of patients to undergo invasive procedures.

In a recent study of more than 100 community-based oncologists, nearly one-third of NSCLC patients were not tested for EGFR or ALK mutations, and more than 75% were not tested for ROS1 fusions. Fewer than 10% of NSCLC patients were tested for all guideline-recommended alterations. These results are similar to a study in a single academic center where 58% of non-squamous NSCLC were tested for EGFR and 40% for ALK fusions, despite repeat invasive biopsies to obtain sufficient tissue for genomic testing in 13% of patients. Tissue availability was similarly limited in several recent series, some of which reported that more than 50% of NSCLC patients had insufficient or unobtainable material for tissue-based CGP.

Even when adequate tissue for NGS testing is available for testing, many specimens do not yield a complete result for a variety of reasons. Pre-analytical variables in tissue preservation are known to impact the quality and success of the NGS testing. Some of these variables include tissue fixation and processing variables, the volume of tissue (needle biopsy or resection specimen) available for testing, and the fraction of tumor cells within the specimen. Evaluating somatic mutations in FFPE (formalin-fixed, paraffin-embedded) tissue below 5% allele frequency is challenging due to these pre-analytical variables.

Recently, the Oncomine™ Dx Target Test (Thermo Fisher Scientific Inc., Waltham, MA) and FoundationOne CDx™ (Foundation Medicine, Cambridge, MA) tissue-based NGS panel assays received FDA approval and Medicare coverage as alternatives to multiple, individual FDA approved companion diagnostics (CDx). The Oncomine panel is considered the least tissue intensive of the CGP tissue profiling panels. In the Oncomine clinical validation studies submitted for FDA approval, only 60% of samples had sufficient tissue for successful testing. The Oncomine validation set included surgical resections specimens that generally have a higher tumor load than diagnostic biopsies and may represent an over-estimate of successful testing specimens.
Currently, a variety of techniques are used to test for genomic alterations in plasma specimens to determine if a patient is a candidate for targeted therapy, including the FDA-approved Cobas® EGFR Mutation Test (tissue or plasma samples) for erlotinib and osimertinib. This assay interrogates specific regions in EGFR to determine whether the genomic alteration of interest is present.\textsuperscript{22} For various reasons, these companion diagnostics (CDx) and other existing lab developed test (LDT) techniques may miss deleterious EGFR mutations, ALK rearrangements, and other genomic alterations that can be targeted with FDA-approved drugs, though efficacy data for the patient’s specific indication may be limited. For example, alterations may occur outside the sequenced region or involve complex alterations (e.g. indels, copy number alterations, or rearrangements) that are not detectable by certain tests.\textsuperscript{22}

Within the InVision clinical validation studies, only 33\% of the prospectively recruited NSCLC patients had sufficient tissue for complete CGP. The remaining 67\% either had no tissue for genomic analysis (31\%) or had only enough tissue for some but not all markers required (36\%). This data underscores the marked limitation of available tissue specimens for tissue CGP testing and emphasizes the importance of plasma-based CGP testing.

Even when successful, tissue acquisition procedures pose a significant morbidity and mortality risk to Medicare patients. In a recent report, 19\% of all lung tissue acquisition procedures resulted in a serious adverse event.\textsuperscript{23} The National Lung Cancer Screening Trial reported 1-2\% mortality rates in their cohorts.\textsuperscript{24}

Given that the majority of lung cancer diagnoses are based on needle biopsy, and that only 30\%-60\% of tissue specimens provide full informative results by CGP, plasma-based CGP (ctDNA testing) identifies genetic alterations for use of targeted therapies without delay in therapy,\textsuperscript{25} and without the risks and costs of repeat invasive biopsy.\textsuperscript{23,26} InVision detects genomic targets linked to targeted drug therapies used at diagnosis and/or progression with response rates similar to those patients identified using tissue-based CGP and tissue-based CDx.

**InVision Test Description and Performance**

InVision is a plasma-based circulating tumor DNA (ctDNA) NGS assay for detection of genomic alterations consisting of 36 commonly mutated genes. It utilizes technology first developed by the Cancer Research UK (CRUK)-funded Cambridge Institute at the University of Cambridge.\textsuperscript{27-29} The group was first to publish industry standard ctDNA methods, including hybrid capture and the highly sensitive tagged amplicon, deep sequencing or TAm-Seq\textsuperscript{TM} technology. The InVision assay utilizes an enhanced version of the TAm-Seq method developed by Inivata to detect clinically relevant cancer mutations of low allele fractions in cell free DNA (cfDNA) including substantial improvements and optimizations to maximize sensitivity and specificity of the assay.\textsuperscript{28}

Approximately 76\% of patients with NSCLC are known to have a genomic alteration in tumor tissue for 1 of 8 genes (EGFR, ALK, ROS1, BRAF, MET, ERBB2, KRAS, STK11).\textsuperscript{30} These alterations constitute actionable driver alterations (EGFR, ALK, ROS1, BRAF, MET, ERBB2 - rule-ins) associated with FDA approved therapies or are recognized as mutually exclusive for actionable changes (STK 11 and KRAS-rule-outs). These alterations have not been described as significant mutations contributing to clonal hematopoiesis of indeterminate potential.\textsuperscript{31}

**Analytical Validation**

The analytical validation of the InVision assay was conducted according to the deliverables outlined in the MolDx document M00135 v2.0. Using contrived samples and tested with multiple users, multiple reagent lots and across multiple days, the sensitivity, specificity, reproducibility and level of detection (LoD) is summarized for all four variant types in the test system: SNV, Structural Variants (SV), Indel, and CNV. Using patient samples, orthogonal comparison to digital PCR/fluorescent in-situ hybridization (dPCR/FISH) techniques was generated for SNVs, Indels and SVs. Interference of somatic mutation detection was investigated with both spiked EDTA or Streck BCT plasma with fragmented cell line DNA and detection was shown to be comparable.
In the analysis of the contrived sample sets (Table 1), the PPA is 96.6% for SVs, 100% for SNVs, 97.4% for Indels and 100% for CNVs. The PPV is 100% for SVs, 99.8% for SNVs, 100% for Indels and 98.3% for CNVs. Specificity was shown to be acceptable for all variants. One CNV false positive was seen. No false positives were seen with Indels or SVs. In normal donor analysis, one SNV is considered to be a false positive. Specific variants described in M00135 were further analyzed for specificity and were shown to be of high specificity (>99% NPA). Reproducibility for all variants as analyzed at the LoD region was shown to be acceptable within reagent lots, within operators, and overall.

### Table 1. Analytical Performance for the InVisionFirst assay

<table>
<thead>
<tr>
<th>Platform</th>
<th>Actionable Alterations</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alteration</td>
<td>Result</td>
<td>Alteration</td>
</tr>
<tr>
<td></td>
<td>EFGFR</td>
<td>SNVs</td>
<td>100% @ &gt;0.25AF</td>
</tr>
<tr>
<td></td>
<td>ALK</td>
<td>Indels</td>
<td>97.4% @ &gt;0.25AF</td>
</tr>
<tr>
<td></td>
<td>ROS1</td>
<td>Fusions</td>
<td>96.6% @ &gt;0.5%</td>
</tr>
<tr>
<td></td>
<td>BRAF</td>
<td>CNVs</td>
<td>98.3% @ 1.5x CNAR</td>
</tr>
<tr>
<td></td>
<td>ERRBB2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MET</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KRAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>STK11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>InVisionFirst™ amplicon-based 36 gene panel</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity for both the detection of contrived samples and patient samples is shown in Table 2. The goals for meeting the lower 95% CI for the M00135 guidance was met at both the LoD region and at the region >3x or 2x LoD. Specific variants described in M00135 were further analyzed for sensitivity and were shown to be of high sensitivity (>97% PPA) in all variants (Table 3). Orthogonal testing,\textsuperscript{32} Table 4, showed very good agreement with dPCR with the region of greatest disagreement between the two technologies occurring at the LoD90-3xLoD90 region. Above the 3xLoD90 region the agreement between dPCR and NGS was 100%. 8/9 ALK or ROS1 fusions were detected where the tissue was shown to be FISH positive for the fusions.\textsuperscript{32}

### Table 2- Performance Characteristics - All Variants Tested Contrived Samples

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>Detail</th>
<th>Unique Samples</th>
<th>Unique Variants</th>
<th>No Calls</th>
<th>Unique Variants by ctDNA</th>
<th>Concordant Unique Variants</th>
<th>Variant-level PPA (95% CI)</th>
<th>Variant-level TPPV (95% CI)</th>
<th>Variant-level Reproducibility (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>VAF =&gt;0.75%</td>
<td>41</td>
<td>519</td>
<td>0</td>
<td>519</td>
<td>519</td>
<td>100% (CI: 0.9963 to 1,000)</td>
<td>99.8% (CI: 0.9911 to 0.9998)</td>
<td>N/A</td>
</tr>
<tr>
<td>SNVs</td>
<td>Expected VAF: 0.25%-0.75% VAF</td>
<td>4</td>
<td>76</td>
<td>0</td>
<td>76</td>
<td>76</td>
<td>100% (CI: 0.9751 to 1,000)</td>
<td>98.7% (CI: 0.9409 to 0.9986)</td>
<td>98.8% (CI: 0.9706-0.9958)</td>
</tr>
<tr>
<td>Indels</td>
<td>≤ 20 bp &gt;0.75% VAF</td>
<td>29</td>
<td>74</td>
<td>2</td>
<td>72</td>
<td>72</td>
<td>97.3% (CI: 0.9161)</td>
<td>100.0% (CI: 0.9161)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Created on 02/06/2020. Page 6 of 15
<table>
<thead>
<tr>
<th>Variant Type</th>
<th>Unique Samples</th>
<th>Samples with Specified Variant Expected</th>
<th>No Calls</th>
<th>Samples with Specified Variant Detected by ctDNA</th>
<th>Concordant &quot;Positive&quot; Samples</th>
<th>Concordant &quot;Negative&quot; Samples</th>
<th>Sample-level PPA (95% CI)</th>
<th>Sample-level NPA (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKL (SVs)</td>
<td>54</td>
<td>54</td>
<td>2</td>
<td>52</td>
<td>52</td>
<td>95</td>
<td>98.1% (0.8865 - 0.9922)</td>
<td>100% (0.9800 - 1.000)</td>
</tr>
<tr>
<td>BRAF (V600E and V600K)</td>
<td>43</td>
<td>43</td>
<td>0</td>
<td>43</td>
<td>43</td>
<td>109</td>
<td>100% (0.9566 - 1.000)</td>
<td>100% (0.9826 - 1.000)</td>
</tr>
<tr>
<td>EGFR (G719A, G719C, G719S, S768I, T791M, L858R, L861Q)</td>
<td>43</td>
<td>43</td>
<td>0</td>
<td>83</td>
<td>83</td>
<td>436</td>
<td>100% (0.9772 - 1.000)</td>
<td>100% (0.9956 - 1.000)</td>
</tr>
<tr>
<td>EGFR (ex on 19 deletions and exon 20 insertions)</td>
<td>43</td>
<td>30</td>
<td>1</td>
<td>40</td>
<td>40</td>
<td>217</td>
<td>97.6% (0.8916 - 0.9974)</td>
<td>99.5% (0.9788 - 0.9995)</td>
</tr>
</tbody>
</table>

Table 3- Performance Characteristics – Specific Variants Tested Contrived Samples
### Table 4 - Performance Characteristics - Orthogonal Testing

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>Detail</th>
<th>Unique Samples</th>
<th>Unique ( \text{VAF} &gt; 0.75% )</th>
<th>Unique ( \text{VAF} = 0.25% - 0.75% )</th>
<th>No Calls</th>
<th>Unique Variants by ( VAF = 0.25% - 0.75% )</th>
<th>Concordant Variants</th>
<th>Variant - level PPA (95% CI)</th>
<th>Variant level APPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNVs</strong></td>
<td></td>
<td>97</td>
<td>43</td>
<td>0</td>
<td>43</td>
<td>43</td>
<td></td>
<td>100% (CI: 0.9566 to 1.000)</td>
<td>100% (CI: 0.9566 to 1.000)</td>
</tr>
<tr>
<td><strong>SNVs</strong></td>
<td></td>
<td>77</td>
<td>15</td>
<td>0</td>
<td>17</td>
<td>12</td>
<td></td>
<td>80% (CI: 0.5564 to 0.9402)</td>
<td>70.6% (CI: 0.4702 to 0.8778)</td>
</tr>
<tr>
<td><strong>Indels</strong></td>
<td>( \leq 20) bp ( &gt; 0.75% ) ( VAF )</td>
<td>56</td>
<td>31</td>
<td>0</td>
<td>31</td>
<td>31</td>
<td></td>
<td>100% (CI: 0.9404 to 0.9999)</td>
<td>100.0% (CI: 0.9404 to 0.9999)</td>
</tr>
<tr>
<td><strong>Indels</strong></td>
<td>( \leq 20) bp ( VAF = 0.25% - 0.75% )</td>
<td>32</td>
<td>7</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td></td>
<td>85.7% (CI: 0.4992 to 0.9841)</td>
<td>100.0% (CI: 0.7358 to 0.9997)</td>
</tr>
<tr>
<td><strong>SVs</strong></td>
<td>Any Detection</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td></td>
<td>88.9% (CI: 0.5855 to 0.9877)</td>
<td>100.0% (CI: 0.7925 to 0.9998)</td>
</tr>
</tbody>
</table>

---

1 CNA not tested with orthogonal method.

2 Neither non-NGS method or NGS method returns quantitative values.

Created on 02/06/2020. Page 8 of 15
Clinical Validation

The InVision test was investigated prospectively in advanced untreated patients with non-squamous NSCLC blood samples. Clinical validation data consists of combined analysis of three studies. Two prospective multicenter studies (NCT02906852 and NCT03116633) demonstrated the concordance of the InVision assay with tissue-based CGP in 254 patients with untreated advanced (stage IIIB/IV) non-squamous NSCLC. A third study consisted of a small group of banked matched tissue and plasma samples (n=10) from an equivalent patient population that were procured from a commercial bio-repository and used to supplement the prospective collections. Across the 264 patients, only 165 patients (62.5%) had tissue available for testing for any point mutations/indels. For 159 patients (60.2%), tissue was tested for ROS1 and/or ALK fusions. 119 patients (45% of patients) underwent CGP.

The performance of InVision is highlighted by the following factors:

- **High Sensitivity**: for each of the key 8 genes used for therapeutic treatment decision with an overall plasma sensitivity of 73.9% (73.9% of tissue results are identified in plasma);
- **High Proportion of Informative Results**: based on the utilization of 8 specific genes (present in tumors independently of each other occurring in 53% of NSCLC) each with individual high gene sensitivity;
- **High Specificity**: for each of the 8 panel genes that supports correct therapeutic determination (CTD) in the 53% of patients with informative results.

Based on literature evidence of the prevalence of the genetic alterations in the 8 genes of most interest (76%) and an assumed 70% clinical sensitivity for ctDNA testing, the authors predicted an informative result in 50% of patients with untreated advanced NSCLC (0.76x0.7). Clinical CTD performance based on InVision profiling results yielded actionable genes in 18.2% of patients and rule out findings in 35.6%, an informative result in 53.8% of patients (95%; CI 41%-56.2%) (Table 5). Of the plasma positive gene results, when either a molecular change in the 6 actionable driver genes (rule-in) or, a non-targetable gene (rule-out) was detected, the correct therapeutic determination (CTD) was 100%. This clinical validity is consistent across the entire intended use population (n=264), both those with and without tissue for profiling.

<table>
<thead>
<tr>
<th>Class</th>
<th>Alterations</th>
<th>Total Enrolled (n=264)</th>
<th>Plasma (%)</th>
<th>Total Enrolled (n=264)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>Tissue</td>
<td></td>
</tr>
<tr>
<td>Rule-In</td>
<td></td>
<td>48</td>
<td>18.18</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>EGFR exons 18-21</td>
<td>26</td>
<td>9.85</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>ALK-ROS1 fusions</td>
<td>5</td>
<td>1.89</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>ERBB2 exon 20</td>
<td>4</td>
<td>1.52</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>insertions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BRAF V600E</td>
<td>6</td>
<td>2.27</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>MET exon 14 splice</td>
<td>7</td>
<td>2.65</td>
<td>6</td>
</tr>
<tr>
<td>Rule-Out</td>
<td>KRAS/STK11</td>
<td>94</td>
<td>35.61</td>
<td>70</td>
</tr>
</tbody>
</table>

Performance characteristics for clinically actionable alterations in 8 genes that effect clinical patient management were: PPV-97.8%, NPV-97.1%, sensitivity-73.9% and specificity-99.8% (Table 6).

Table 5: InVision - ctDNA Clinical Validity

Table 6: Concordance of Combined and Individual Actionable Driver Genomic Alterations

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tissue</th>
<th>Liquid</th>
<th>No call</th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
</table>

Created on 02/06/2020. Page 9 of 15
Clinical Utility

Clinical utility has been demonstrated with prospective outcome collection from within the clinical validation study and within additional studies at the Institute Gustave Roussy (Paris, France) and Centre Leon Berard (Lyon, France), and in 3 groups of patients; namely,

1. Patients not exposed to any prior therapy and receiving targeted therapy directed by the assay
2. Patients with no prior targeted therapy but other therapy and targeted directed by the assay, and
3. Patients with prior anti-EGFR targeted therapy and now progressing with the specific osimertinib sensitive mutation T790M detected by the assay.

As detailed recently by the FDA, time on treatment was used as the endpoint for clinical impact of targeted therapy. When targeted therapies are used in patients without a specific target, average time on treatment is well under 2 months. With current directed targeted treatment in NSCLC, it is unusual to come off therapy before 3 months. Regardless of which group mentioned above was assessed, disease control at 3 months was approximately 80% or more, which is equivalent to the best outcomes of any target agent reported. This is strong evidence that therapeutic determination based on InVision results is equivalent to outcomes reported in clinical trials, and most importantly unlikely to be causing patient harm (Table 7).

Implied clinical utility of Inivata’s prospective clinical validation study (NCT02906852) and three unpublished internal studies identified actionable alterations in patients who received FDA approved drugs and tracked clinical outcomes (Table 7).

Table 7: Actionable Genomic Alterations Detected by InVision:

<table>
<thead>
<tr>
<th>Genomic alteration</th>
<th>n</th>
<th>Number still on targeted therapy at 3 months</th>
<th>% still on targeted therapy at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK/ROS1 fusions</td>
<td>2</td>
<td>292</td>
<td>100.0</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>5</td>
<td>140</td>
<td>100.0</td>
</tr>
<tr>
<td>EGFR (exons 18-21)</td>
<td>13</td>
<td>146</td>
<td>96.7</td>
</tr>
<tr>
<td>ERBB2 exon 20 ins</td>
<td>2</td>
<td>137</td>
<td>100.0</td>
</tr>
<tr>
<td>KRAS</td>
<td>48</td>
<td>86</td>
<td>80.0</td>
</tr>
<tr>
<td>MET exon 14 splice</td>
<td>3</td>
<td>133</td>
<td>100.0</td>
</tr>
<tr>
<td>STK11</td>
<td>15</td>
<td>93</td>
<td>71.4</td>
</tr>
<tr>
<td>Key 8 genes*</td>
<td>88</td>
<td>1027</td>
<td>73.9</td>
</tr>
<tr>
<td>All Genes</td>
<td>156</td>
<td>4135</td>
<td>70.6</td>
</tr>
</tbody>
</table>

*“Key 8 genes” refers to the combination of all directly actionable mutations (ALK/ROS1 fusions, BRAF V600E, EGFR exons 18-21, ERBB2 insertions, MET exon 14 splice) and KRAS and STK11 variants.
Professional Society Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN) clinical practice guidelines (v4.2018) for non-small cell adenocarcinoma recommend a broad molecular profile panel. NCCN recommends molecular testing in never-smokers regardless of histology or mixed histology, and in small biopsies with the goal of identifying rare driver mutations for which effective drugs may be available. Tissue profiling is recommended to include EGFR and ERBB2 point mutations and indels; BRAF mutations; ALK, ROS1, and RET rearrangements; and MET amplification and deletion/skipping of exon. The guidelines indicate that if tissue biopsy is not feasible, plasma biopsy should be considered. If plasma biopsy is negative, then repeat tissue biopsy is recommended, if feasible. 

Analysis of Evidence
(Rationale for Determination)

Level of Evidence:

Quality – Moderate
Strength – Limited
Weight – Limited

The InVision assay provides a minimally invasive methodology to detect actionable mutations with an informative test rate of 50-70% for providing valuable guidance for patient genomic profile stratification. Clinical utility has been demonstrated equivalent to tissue-based profiling outcomes. Patients are limited to one test assay per primary diagnosis.
Bibliography


19. Morris, Scott, Janakiraman Subramanian, Esma Gel, George Runger, Eric Thompson, David Mallery, and Glen Weiss. “Performance of Next-Generation Sequencing on Small Tumor Specimens and/or Low Tumor Content Samples Using a Commercially Available Platform.” *PloS One* 13, no. 4 (2018): e0196556. [https://doi.org/10.1371/journal.pone.0196556](https://doi.org/10.1371/journal.pone.0196556)


### Revision History Information

<table>
<thead>
<tr>
<th>REVISION HISTORY DATE</th>
<th>REVISION HISTORY NUMBER</th>
<th>REVISION HISTORY EXPLANATION</th>
<th>REASON(S) FOR CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/01/2019</td>
<td>R2</td>
<td>The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.</td>
<td>• Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</td>
<td></td>
</tr>
<tr>
<td>11/01/2019</td>
<td>R1</td>
<td>As required by CR 10901, all billing and coding information has been moved to the companion article; this article is linked to the LCD.</td>
<td>• Revisions Due To Code Removal</td>
</tr>
</tbody>
</table>

### Associated Documents
Attachments

N/A

Related Local Coverage Documents

Article(s)
A57664 - Billing and Coding: MolDX: Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer
A56411 - Response to Comments: MolDX: Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer

LCD(s)
DL37897 - MolDX: Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer

Related National Coverage Documents

N/A

Public Version(s)

Updated on 01/29/2020 with effective dates 11/01/2019 - N/A
Updated on 10/24/2019 with effective dates 11/01/2019 - N/A
Updated on 04/11/2019 with effective dates 06/03/2019 - N/A

Keywords

- Inivata
- InVisionFirst
- Liquid Biopsy
- Lung cancer
- EGFR
- single nucleotide variants
- SNVs