Local Coverage Determination (LCD):
MolDX: BDX-XL2 (L37062)

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

Contractor Information

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<tr>
<th>CONTRACTOR NAME</th>
<th>CONTRACT TYPE</th>
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LCD Information

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Document Information

**LCD ID**
L37062

**LCD Title**
MoIDX: BDX-XL2

**Proposed LCD in Comment Period**
N/A

**Source Proposed LCD**
DL37062

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**Retirement Date**
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**Notice Period Start Date**
08/14/2017

**Notice Period End Date**
09/28/2017
or Laryssa Marshall at (312) 893-6814. You may also contact us at ub04@healthforum.com.

**CMS National Coverage Policy**

Title XVIII of the Social Security Act, §1862(a)(1)(A). Allows coverage and payment for only those services that are considered to be reasonable and necessary.

Title XVIII of the Social Security Act, §1833(e). Prohibits Medicare payment for any claim which lacks the necessary information to process the claim.


CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

CMS Internet-Only Manuals, Publication 100-04, Medicare Claims Processing Manual, Chapter 16, §50.5 Jurisdiction of Laboratory Claims, 60.12 Independent Laboratory Specimen Drawing, 60.2. Travel Allowance.

CMS Internet Online Manual Pub. 100-04 (Medicare Claims Processing Manual), Chapter 23 (Section 10) "Reporting ICD Diagnosis and Procedure Codes".

**Coverage Guidance**

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

This Medicare contractor will provide limited coverage for the (BDX-XL2) test (Biodesix, Boulder, CO and Seattle, WA) for the management of a lung nodule, between 8 and 30mm in diameter, in patients 40 years or older and with a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less. The intended use of the test is to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign. These lung nodules would then be candidates for non-invasive computed tomography (CT) surveillance instead of invasive procedures.

**Summary of Evidence**

**Coverage Summary**

The BDX-XL2 assay is reasonable and necessary to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign. This assay is only covered when the following conditions are met:

- Patient is at least 40 years of age and has a lung nodule of diameter 8 to 30mm, and
- The pre-test risk of cancer as determined by the Mayo risk prediction algorithm (10) is 50% or less.

Note: The BDX-XL2 test should not be ordered if a physician does not intend to act upon the test result. It is expected that physicians will advise nodule surveillance for at least 80% of patients with a post-test probability of 98% or higher.
Lung nodules are rounded densities, under 30mm in diameter, detected by chest radiograph (CXR) or computer tomography (CT) scan. Nodules are mostly surrounded by lung tissue and are also called coin lesions, solitary pulmonary nodules or lesions, or a “spot” on the lung. The edges of a nodule can be described as smooth or irregular (stellate or spiculated) with irregular edges somewhat more indicative for cancer. Heavily calcified nodules with smooth edges are generally benign and solid nodules that have not shown growth over time are considered benign. For a comprehensive review of nodules and their evaluation see the 2-part series by Patel, et al.\textsuperscript{1, 2}

Lung nodules are detected incidentally or through lung cancer screening. Lung cancer screening now has Medicare coverage in the United States. As of April 26, 2016 there were 806 sites registered for screening (http://www.acr.org/quality-safety/national-radiology-data-registry/lung-cancer-screening-registry – see Core Documents, accessed June 20, 2016). The estimated number of new lung nodules incidentally detected annually in the US is 1.57 million whereas it is anticipated that another 1.5 million are detected by screening annually in the US.\textsuperscript{3}

Early detection of lung nodules is an opportunity to reduce lung cancer mortality but it comes with significant risks. These risks are both for patients and health care delivery networks. For patients, a major problem is the risk of unnecessary invasive procedures to find the minority of nodules that are cancer. For health care delivery, the risks are both costs and overloading the health care system.

Of the expected 3 million nodules per year found incidentally or by lung cancer screening, the majority will be Medicare age. Four recent studies underscore the importance of lung cancer evaluations to the Medicare population:

- The mean age of 377 eligible patients in an 18 site retrospective chart review study was 65.\textsuperscript{4}
- A prospective study across 12 sites and 475 patients found 62.5% of patients were 65 years of age or older.\textsuperscript{5}
- A recent study reported that between Jan 2009 and Dec 2011, 8,979 Medicare patients from a random sampling of 5% of Medicare claims, underwent lung cancer evaluations because of an abnormal chest CT scan.\textsuperscript{6}
- In the National Lung Screening Trial (NLST), over 57% of enrollees were over 65 years of age.\textsuperscript{7} Also the rates of nodule detection increased dramatically with age.\textsuperscript{3} Medicare enrollees are more likely to meet lung cancer screening criteria and have more nodules detected.

A set of guidelines for lung nodule management is published and updated by the American College of Chest Physicians (ACCP). The ACCP guidelines for lung nodules, updated in 2013, is the primary reference used by pulmonologists in the United States.\textsuperscript{8} The ACCP Guidelines state: “Although clinical and radiographic [CT scans] characteristics cannot reliably distinguish between benign and malignant nodules in most individuals, it is nevertheless important to estimate the clinical probability of malignancy before ordering imaging tests or biopsy procedures”. The pretest probability of malignancy (pCA) is estimated by using clinical judgment or with a quantitative risk model.\textsuperscript{9, 10} Establishing a pCA creates three risk stratification groups, namely, Low, Intermediate, and High probability, with Low risk having pCA below 5% and High risk having pCA above 65%. The general concept is that Low risk patients will be observed with CT surveillance to watch for growth if a nodule is malignant. Conversely, the guidelines suggest those patients in the High risk group go directly to surgery. The logic is that the probability of cancer is high enough that a negative biopsy will not change the care pathway. The Intermediate risk group (5-65% pCA) are recommended to enter the diagnostic odyssey that often includes PET scanning as the next step. A negative PET suggests a benign nodule, so the patient is followed with CT scans. A positive PET scan goes on to surgery or biopsy. This is the overall concept, but PET has sensitivity and specificity challenges. In particular, current estimates of PET
sensitivity from 72% to 94% and is reviewed in the 2013 ACCP Guidelines in section 4.2.3.\textsuperscript{8} False positive PET scans for nodules are an additional problem with estimates of the false positive PET scan rate of 39%.\textsuperscript{4}

A pulmonary community practice observational chart review of 18 practices and 377 patients found a wide variation in management of nodules.\textsuperscript{4} The surgery rate for benign nodules was 35% and the rate of surgery was the same for Low, Intermediate and High risk patients. The risk categories were calculated by the study and despite a Low risk, 28% had biopsies and 17% had surgery. The rates of surgery for benign nodules range between 10% and 55%. A survey of 196 pulmonologists supports the potential of a non-invasive biomarker to positively improve lung nodule management decisions.\textsuperscript{11}

Biopsies can be obtained through a bronchoscope or a needle passed through the chest wall with CT image guidance. A community practice chart review found 38% of patients had a form of biopsy.\textsuperscript{4} Complications with biopsies or surgery are increased with age, smoking history, and other lung disease. Biopsy through the bronchoscope has the lowest risk with a 2-4% risk of bleeding or pneumothorax.\textsuperscript{8} A disadvantage of this procedure is inaccurate sampling of the nodule. Correct sampling averages about 50%.\textsuperscript{8} The correct sampling rate may improve with modern navigation techniques that are being adopted. Bronchoscopic biopsy use for nodules is currently about 20% of nodules.\textsuperscript{6} Needle biopsies are done in about 15% of patients with nodules with a 1% risk of bleeding, and a 15-19% risk of pneumothorax.\textsuperscript{12} About half (7%) of patients with a pneumothorax require chest tube placement with a significant period of hospitalization.\textsuperscript{12} Most needles biopsies are diagnostic but the risk of a non-diagnostic result with a malignant nodule is about 20%.\textsuperscript{8} Biopsies (combined bronchoscopy and needle) are performed in about 25% of nodules (200,000) and the procedures are for benign nodules in 42-62% (104,000). Complications from biopsies result in hospitalization in 2-7% of cases.\textsuperscript{6,12} That translates into 4,680 excess hospitalizations per year that are potentially avoidable.

Eventually, most malignant nodules go to surgery for resection and about 15-25% of patients have biopsy attempts before surgery. The overall surgery rate is about 34% (270,000 per year) for benign and malignant nodules in the nodule population.\textsuperscript{4} Complications include death (2% in Medicare population),\textsuperscript{13} prolonged lung air leak (3-5%), and pneumonia (1-8%).\textsuperscript{8} Published rates for surgery for benign nodules range from 31-44%.\textsuperscript{4,7,17} This translates into an estimated 102,000 surgeries and 2,052 deaths per year that are avoidable for patients that do not have lung cancer.

**Test Description and Intended Use**

BDX-XL2 is a proteomic risk predictor that integrates the expression levels of two proteins with five clinical risk factors. The BDX-XL2 assay is performed on fresh-frozen EDTA plasma samples using mass spectrometry.\textsuperscript{15,16} Results are reported as “Likely Benign” when the post-test probability that a lung nodule is benign is 90% or higher. Otherwise, the test reports “Indeterminate” when the post-test probability is less than 90%. “Likely Benign” test reports also include the post-test probability that the lung nodule is benign, ranging from 90% to 98%. This is further detailed in Table 1 below along with the performance of the test at each post-test probability.

The intended use of the test is to assist physicians in the management of lung nodules by identifying those lung nodules with a high post-test probability of being benign. These lung nodules would then be candidates for non-invasive computed tomography (CT) surveillance instead of invasive diagnostic procedures such as biopsy or surgery.

**Clinical Validation**
The discovery, clinical validation and analytical performance of earlier versions of the assay were previously reported.\textsuperscript{15-17} The current version of (BDX-XL2) is a refinement that incorporates clinical risk factors (nodule size, age, smoking history, nodule location and nodule spiculation). BDX-XL2 was retrospectively validated on the prospective observational PANOPTIC study (NCT01752114) of lung nodule management.\textsuperscript{18} PANOPTIC enrolled 685 subjects across 33 sites in the US and Canada. Validation of BDX-XL2 followed the National Academy of Medicine’s guidelines for rigorous test development.\textsuperscript{19}

In the PANOPTIC study, 178 subjects met the intended use population of BDX-XL2. This consisted of 149 benign lung nodules (as determined by histopathology after biopsy or surgery, or by stable CT surveillance of a lung nodule after at least 1 year) and 29 malignant lung nodules (as determined by histopathology after biopsy or surgery), yielding a cancer prevalence of 16.3%. Per protocol, this cohort of patients was split into separate verification (n = 69) and validation (n = 109) subsets, with pre-specified interim and final analyses on each subset, respectively, to determine the performance characteristics of the test. Since the test system and clinical endpoints were unchanged between the interim and final analyses, all analyses were blinded, and the 2 patient cohorts were mutually exclusive, the 69 and 109 patients are combined below.

For these 178 subjects, BDX-XL2 yielded a sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of 97% (CI: 82%-100%), 44% (CI: 36%-52%), 98% (CI: 92%-100%), and 25% (CI: 17%-34%), respectively. We note that the post-test probability of BDX-XL2 is equivalent to its NPV.

Procedure use and clinical factors were collected in the PANOPTIC study permitting the comparison of BDX-XL2 performance to:

- current practice, as characterized by physician pre-test risk assessment, denoted as pCA, which is based on the physician’s clinical assessment of risk using a clinical risk model and/or clinical judgement,
- PET, and
- clinical risk factor models including the 'Mayo', 'VA', 'Brock' and 'Herder' models (9, 10, 19, 20).

Using AUC as a general performance measure, the respective AUCs for BDX-XL2, pCA, PET, and these four clinical factor models were: 76% (CI: 69%-82%), 69% (CI: 62% - 76%), 58% (CI: 46%-69%), 69% (CI: 62%-76%), 60% (CI: 53%-67%), 71% (CI: 63%-77%), and 67% (CI: 56%-78%). BDX-XL2 had statistically significant improved performance over all above diagnostic modalities with p-values 2.1xE-11 (pCA), 0.001 (PET), 0.0009 (Mayo), 2.7xE-7 (VA), 0.005 (Brock) and 0.02 (Herder).

\textbf{Clinical Utility}

Current practice has been previously characterized\textsuperscript{4, 11} as well as the potential clinical utility of an earlier version.\textsuperscript{5} The clinical utility of BDX-XL2 is measured in terms of its potential to reduce unnecessary invasive procedures, such as biopsies and surgeries, on benign lung nodules while not significantly increasing the number of malignant lung nodules routed to CT surveillance thereby delaying surgical resection. Assuming strict adherence to management recommendations based on assay results (i.e., active surveillance if “likely benign”), an earlier version of Xpresys Lung demonstrated a potential 32% reduction in invasive procedures on benign lung nodules without increasing the number of malignant nodules routed to CT surveillance\textsuperscript{5} based on a retrospective analysis of a prospective observational study of lung nodule management (NCT01752101). Similarly, in the PANOPTIC study, the potential clinical utility of the current version of (BDX-XL2) was assessed retrospectively. Specifically, if BDX-XL2 were used to guide lung management (and assuming a post-test probability of 98%), then invasive procedures on benign lung nodules would have been reduced 36% (CI: 22%-52%) with only 3% (CI: 0%-18%) of malignant nodules routed to CT
surveillance (compared to 45% with current practice in the PANOPTIC study).

## Summary of Analytical and Clinical Performance

### General

BDX-XL2 is intended for the evaluation of 8-30 mm lung nodules in patients 40 years or older with a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less.

### Intended Use

Plasma from K2 EDTA vacutainer tubes

### Analytical Performance

<table>
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<tr>
<th>Description</th>
<th>Results (with 95% Confidence Intervals if applicable)</th>
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<td><strong>Repeatability (within run precision)</strong></td>
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<tr>
<td>8 samples tested three times within a run, 1 instrument, 2 operators, 3 runs, 3 non-consecutive days, 1 manufacturing reagent lot for critical reagents. Qualitative results represent only 2 possible final results (i.e., indeterminate and likely benign) with post-test probabilities for the latter from 90 to 98%.</td>
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<td><strong>Intermediate precision (between run precision)</strong></td>
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<td>7 samples tested once in three different runs, 1 instrument, 2 operators, 3 runs, 3 non-consecutive days, 1 manufacturing reagent lot for critical reagents. Qualitative results represent only 2 possible final results (i.e., indeterminate and likely benign) with post-test probabilities for the latter from 90 to 98%.</td>
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<td><strong>Reproducibility (between sites)</strong></td>
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<td><strong>Limit of blank (LOB)</strong></td>
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<td><strong>Limit of detection (LOD)</strong></td>
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<td><strong>Limits of quantitation (LOQ)</strong></td>
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### Analytes (analytical repeatability):

\[
\text{ARR}_{LG3BP} \ CV = 7.0\% \ (3.6\%-10.3\%)
\]

\[
\text{ARR}_{C163A} \ CV = 5.9\% \ (3.6\%-8.2\%)
\]

### Score (analytical repeatability):

\[
\text{Score} \ CV = 9.0\% \ (3.4\%-14.6\%)
\]

### Qualitative (clinical concordance):

62.5% (5/8; 24.5%-91.5%)

**ARR** is defined as the ratio between the peak area for the endogenous quantifier peak and the peak area of the corresponding SIS peptide, multiplied by a calibration factor that is specific for each SIS lot.

**Score** is defined as Log2[\[ARR_{LG3BP}/ ARR_{C163A}\]]

### Analytes (analytical repeatability):

\[
\text{ARR}_{LG3BP} \ CV = 14.5\% \ (10.1\%-18.9\%)
\]

\[
\text{ARR}_{C163A} \ CV = 12.8\% \ (9.1\%-16.6\%)
\]

### Score (analytical repeatability):

\[
\text{Score} \ CV = 6.0\% \ (3.7\%-8.4\%)
\]

### Qualitative (clinical concordance):

85.7% (6/7; 42.1%-99.6%)

**Not applicable**

20 µL plasma

Defined as the upper 99.5% confidence interval (CI) for the response ratio (ARR) observed in negative controls. The lower limit of response for each analyte in samples and positive controls is defined as the lower limit of quantification.

The lower limit of quantification (LLOQ) is defined as the...
lowest response ratio within the linear range where the coefficient of variation (CV) was equal to or below 0.20, where linearity was established using five replicate measures at each concentration.

The upper limit of quantification (ULOQ) is defined as the highest response ratio within the linear range where the coefficient of variation (CV) was equal to or below 0.20, where linearity was established using five replicate measures at each concentration.

LG3BP:
ULOQ = 42
LLOQ = 0.043

C163A:
ULOQ = 71
LLOQ = 0.053

Not applicable for qualitative interpretation (i.e., likely benign or indeterminate)

Linearity
For individual analytes, the linear response range was established between the LLOQ and ULOQ
Visual inspection to detect hemolysis (≥ 100 mg/dL of hemoglobin rejected).

Interfering substances
MRM-MS chromatograms for each analyte in every sample are inspected for interference, with any interference resulting in QC failure.

Specimen stability, primary (EDTA whole blood)
3 hours at 2-8 °C based on validation study (manuscript in preparation)
24 months at -70 °C based on validation study (manuscript in preparation)

Specimen stability, intermediate (plasma)
2 freeze-thaw cycles when stored at -70 °C based on validation study (manuscript in preparation)
24 months at -70 °C for 2 critical reagents (i.e., Human Plasma Samples (HPS) and SIS peptides). ARR for 623 samples evaluated with slope not significantly different from zero (p = 0.77).

Reagent closed/shelf-life stability
Non-critical (general purpose) reagents are stored and expired per manufacturer recommendations.
Critical reagents: Not applicable since single use aliquots

Reagent open/in use stability
Non-critical reagents are stored and expired per manufacturer recommendations.

**Clinical Performance: Validity**

BDX-XL2 integrates the relative abundance of two plasma proteins (LG3BP and C163A) with five clinical risk factors (age, smoking status, nodule diameter, nodule spiculation status and nodule location). From these seven markers, a numerical value, XL_2(k), for a patient k, is calculated.
XL_2(k) ranges between 0 and 1 and its value is used to index the post-test probability (i.e., NPV) validated in the PANOPTIC study (see Table 1 below).

<table>
<thead>
<tr>
<th>XL_2(k) Value</th>
<th>Post-Test Benign Probability (i.e. NPV) (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>Test Report</th>
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<tr>
<td>0 to 0.131</td>
<td>98% (92% - 100%)</td>
<td>97% (82% - 100%)</td>
<td>44% (36% - 52%)</td>
<td>25% (17% - 34%)</td>
<td>Likely Benign</td>
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<tr>
<td>&gt;0.131 to 0.1613</td>
<td>97% (91% - 100%)</td>
<td>93% (77% - 99%)</td>
<td>49% (41% - 57%)</td>
<td>26% (18% - 36%)</td>
<td>Likely Benign</td>
</tr>
<tr>
<td>0.1613 to 0.172</td>
<td>96% (90% - 99%)</td>
<td>90% (73% - 98%)</td>
<td>54% (45% - 62%)</td>
<td>27% (19% - 37%)</td>
<td>Likely Benign</td>
</tr>
<tr>
<td>&gt;0.172 to 0.176</td>
<td>95% (89% - 99%)</td>
<td>86% (68% - 96%)</td>
<td>55% (47% - 63%)</td>
<td>27% (18% - 37%)</td>
<td>Likely Benign</td>
</tr>
<tr>
<td>&gt;0.176 to 0.1785</td>
<td>94% (87% - 98%)</td>
<td>83% (64% - 94%)</td>
<td>56% (47% - 64%)</td>
<td>27% (18% - 37%)</td>
<td>Likely Benign</td>
</tr>
<tr>
<td>&gt;0.1785 to 0.193</td>
<td>93% (86% - 98%)</td>
<td>79% (60% - 92%)</td>
<td>57% (44% - 65%)</td>
<td>26% (18% - 37%)</td>
<td>Likely Benign</td>
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<tr>
<td>&gt;0.193 to 0.195</td>
<td>92% (85% - 96%)</td>
<td>76% (56% - 90%)</td>
<td>58% (49% - 66%)</td>
<td>26% (17% - 37%)</td>
<td>Likely Benign</td>
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<tr>
<td>&gt;0.195 to 0.2306</td>
<td>91% (84% - 96%)</td>
<td>69% (49% - 85%)</td>
<td>64% (56% - 72%)</td>
<td>27% (18% - 39%)</td>
<td>Likely Benign</td>
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<tr>
<td>&gt;0.2306 to 0.354</td>
<td>90% (84% - 95%)</td>
<td>55% (36% - 74%)</td>
<td>83% (75% - 88%)</td>
<td>38% (24% - 54%)</td>
<td>Likely Benign</td>
</tr>
<tr>
<td>&gt;0.354</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>

Clinical Performance: Utility

PANOPTIC was a non-interventional study; however, the potential clinical utility of BDX-XL2 can be estimated by evaluating how many benign (benefit) and malignant (harm) nodules would have been routed away from invasive procedures into CT surveillance if BDX-XL2 had been used to guide patient management in the study (and assuming complete compliance). Table 2 summarizes the potential clinical utility of BDX-XL2 at each post-test probability.

<table>
<thead>
<tr>
<th>Probability of Being Benign</th>
<th>Probability of Benign Nodules (95% CI)</th>
<th>CT Surveillance (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>98%</td>
<td>15/42 = 36% (22% - 52%)</td>
<td>1/29 = 3% (0% -18%)</td>
</tr>
<tr>
<td>97%</td>
<td>17/42 = 40% (26% - 57%)</td>
<td>2/29 = 7% (1% -23%)</td>
</tr>
<tr>
<td>96%</td>
<td>19/42 = 45% (30% - 61%)</td>
<td>2/29 = 7% (1% -23%)</td>
</tr>
<tr>
<td>95%</td>
<td>20/42 = 48% (32% - 64%)</td>
<td>2/29 = 7% (1% -23%)</td>
</tr>
<tr>
<td>94%</td>
<td>20/42 = 48% (32% - 64%)</td>
<td>2/29 = 7% (1% -23%)</td>
</tr>
<tr>
<td>93%</td>
<td>22/42 = 52% (32% - 64%)</td>
<td>3/29 = 10% (1% -23%)</td>
</tr>
</tbody>
</table>
Table 2: Potential Clinical Utility of BDX-XL2

In the PANOPTIC study, there were 178 intended use subjects (when the verification and validation sets are combined) of whom 29 had malignant lung nodules and 149 had benign lung nodules. Of the 149 benign lung nodules, 42 had at least one invasive procedure. Hence the denominator of “42” in column 2 of Table 2. Of the 29 malignant lung nodules, 13 were routed to CT surveillance. That is, 13/29 = 45% of malignant nodules were routed to CT surveillance in PANOPTIC. This is substantially larger than the largest corresponding value in Table 2 (i.e. 24%).

**Analysis of Evidence**

**Rationale for Determination**

**Level of evidence**

Quality – Moderate  
Strength – Moderate  
Weight - Limited

This contractor recognizes that evidence of clinical utility for the (BDX-XL2) assay for ≥40 year old patients with an 8 to 30mm lung nodules and a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of ≤50% is promising at the current time. Clinical studies underway at this time are expected to demonstrate clinical utility. These studies are designed to show a statistically significant reduction in the number of benign lung nodules experiencing invasive procedures between a prospective group of patients managed by BDX-XL2 and a contemporaneous group not managed by BDX-XL2. A secondary end-point will show that the management of lung nodules by BDX-XL2 does not (i.e., is statistically non-inferior to) the number of malignant nodules routed to CT surveillance (determined at one year interval) as compared to current practice without BDX-XL2. Continued coverage for BDX-XL2 testing will be dependent on annual review of prospective data and peer-reviewed studies.

Data collected by Biodesix through ongoing studies will support utility including:

- All clinical risk factors to calculate the Mayo, VA, and Brock cancer risk predictors;
- PET result (if used),
- Physician-assessed pre-test cancer risk assessment,
- Physician post-test lung nodule management recommendation,
- Any subsequent procedures (non-invasive or invasive), and
- Clinical diagnosis based on those procedures (i.e., benign or malignant).

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**General Information**
Bibliography

15. X. J. Li et al., An integrated quantification method to increase the precision, robustness, and resolution of protein measurement in human plasma samples. Clinical proteomics 12, 3 (2015).
18. G. Silvestri et al., Assessment of Plasma Proteomics Biomarker’s Ability to Distinguish Benign From Malignant Lung Nodules: Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial. Chest. 2018 Mar 1


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## 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>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>
| 01/01/2019            | R1                     | Changed the title of the LCD to BDX-XL2 and all Xpresys references to BDX-XL2. Removed "The test is ordered by a physician certified in the XL2 Certification and Training Registry (CTR), and"  
                          | The following information is recorded: all clinical risk factors to calculate the Mayo, VA, and Brock cancer risk predictors; PET result (if used), physician pre-test risk assessment, physician post-test lung nodule management recommendation, any subsequent procedures (non-invasive or invasive), and clinical diagnosis based on those procedures (i.e., benign or malignant)" from the Coverage Summary section.  
                          | Added additional data collected by Biodesix information to the Analysis of Evidence section. Changed the Level of evidence strength from Limited to Moderate. Added reference #18.  
                          | Corrected a typographical error in the Analysis of Evidence sentence, "This contractor recognizes that evidence of clinical utility for the (BDX-XL2) assay for ≥40 year old patients with an 8 to 30mm lung nodules and a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of ≤50% is promising at the current time." Pervious versions indicated "≥40 year old patients" and "of ≤50%," however in the last revision the "≤" and "≥" symbols were inadvertently replaced with "=." Removed a reference to Xpresys and replaced it with BDX-XL2 in the Clinical Validation section.  
                          | Removed 81599 in CPT/HCPCS Group 1 and added 0080U. This revision is due to the 2019 Q1 CPT/HCPCS Updates and is effective 1/1/2019.                                                                 | Creation of Uniform LCDs With Other MAC Jurisdiction  
                          |                                                                                                                                  | Revisions Due To CPT/HCPCS Code Changes                                                                       |