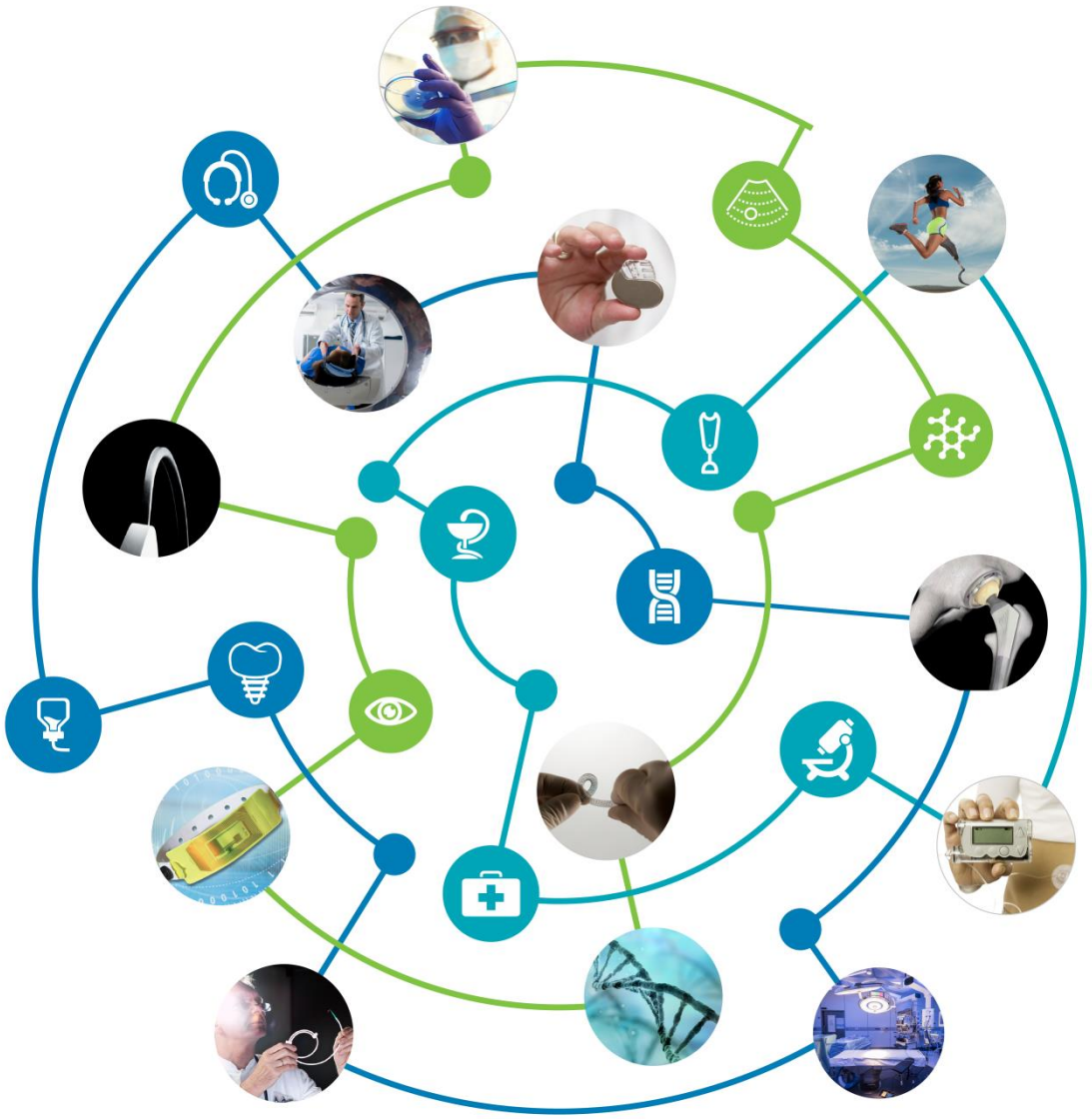
AdvaMedDx Value Assessment Framework *in Practice*



Application of the Comprehensive Assessment of the Value of Diagnostic Technologies Framework to Abbott's Vysis ALK Break Apart FISH Probe Kit Test

Abbott

AdvaMedDx
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Value Framework Overview

In response to the growing need to demonstrate how diagnostic tests and technologies fit into the emerging value-based paradigm for providers, payers, and patients, AdvaMedDx launched a Strategic Value Initiative to develop an approach to value assessment for diagnostic tests and technologies that can be used by Medical technology companies as well as by health systems, payers, and other stakeholders.[1]

The AdvaMedDx Value Assessment approach goes beyond traditional Health Economic Outcomes Research (HEOR) and clinical efficacy metrics to assess the value that diagnostic tests and technologies may contribute to improving patient care and experience, economic outcomes, and the overall health of populations. This approach uses four broad categories, or "value drivers," to describe the value of diagnostic tests and technologies: clinical impact, non-clinical patient impact, care delivery revenue and cost impact, and public/population impact relevant to an array of stakeholders who may evaluate and measure value differently.

The AdvaMedDx Value Assessment approach can be used to guide the development of a value proposition that successfully communicates the full breadth of expected impacts offered by diagnostic tests and technologies while taking into account the demands of the changing health care ecosystem. The collection of information associated with the value drivers reflects quantitative and qualitative metrics of value, gives appropriate weight to patient experience and societal impacts, and also accounts for the consideration of evidence collected through a variety of methods. An illustration highlighting the value drivers and components of AdvaMed's approach is on the following page.

In order to demonstrate the application of this framework across different types of diagnostic tests and technologies, AdvaMedDx has partnered with member companies to develop use cases. These use cases address the clinical need for the diagnostic test or technology, alternative and existing technologies on the market, the expected impacts of the diagnostic test or technology, and the evidence to support such a value assessment. The use cases have been developed as a way to directly demonstrate the application of the AdvaMedDx Value Framework to the featured diagnostic test and should not be construed as an endorsement or promotion thereof.

Abbott

This use case demonstrates the value of Abbott's Vysis ALK Break Apart FISH Probe Kit across all of the identified value drivers and for a range of stakeholders. The Vysis ALK Break Apart FISH Probe Kit is a qualitative DNA-based test intended to aid in the identification of patients eligible for treatment with Xalkori® (crizotinib).

Illustration of AdvaMedDx Value Assessment Approach

Source: "A Framework for Comprehensive Assessment of the Value of Diagnostic Tests", co-developed with Deloitte Consulting LLP

Abbott Vysis ALK Break Apart FISH Probe Kit Test

Diagnostic test developers with a new product concept in development should start early, not only to address the FDA requirements, but also the value proposition that the diagnostic test conveys to patients, providers, and the health care system.

The Abbott Vysis ALK Break Apart FISH Probe Kit demonstrates value across all of the drivers. It also serves as an example of the appropriate application of the AdvaMedDx value assessment approach in establishing value for a range of stakeholders.

The Abbott Vysis ALK Break Apart FISH Probe Kit is an FDA-approved assay that aids in the identification of patients eligible for treatment with Xalkori® (crizotinib). The Abbott ALK Break Apart FISH Probe Kit informs treatment decisions and reduces unnecessary treatment, and the associated side effects, in those for whom Xalkori® (crizotinib) will not be effective.

Unmet Need

AdvaMedDx's assessment process begins with understanding and addressing the unmet need and value imparted through the new diagnostic test.

Unmet patient need can be framed in terms of clinical validity, clinical utility, access, patient preferences, costs, quality of care, ease of use, etc.

Lung cancer is the second most common cancer and the leading cause of cancer death in both men and women. The American Cancer Society expects there to be approximately 222,500 new cases and 155,870 deaths from lung cancer in 2017. [2]

Lung cancer is divided into two main categories— non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 85% of lung cancers and has significantly different treatment regimens and prognoses than SCLC.[3] NSCLC is divided into three subtypes, which all start from different types of lung cells but have similar treatments and outlooks – adenocarcinoma, squamous cell (epidermoid) carcinoma, and large cell (undifferentiated) carcinoma.

About 5% of individuals with NSCLC have a genetic mutation involving the ALK (anaplastic lymphoma kinase) gene.[4] This mutation causes abnormalities in the ALK protein that allow cells to grow and spread uncontrollably and is most often present in non-smokers with adenocarcinoma.[5] The ALK protein can be targeted by certain drugs that can be used after chemotherapy has stopped working or instead of chemotherapy. Xalkori® (crizotinib) is an oral receptor tyrosine kinase inhibitor indicated for use in patients with locally advanced or metastatic NSCLC that is ALK-positive.

Patient Populations

Assessments should consider the extent to which a diagnostic test may be more or less effective for various patient populations and align with the population focus of the stakeholder evaluating the test.

This section demonstrates the value of the diagnostic test to patients by addressing the need for the test in the context of the affected patient sub-population and the available alternatives to treat their condition.

The Vysis ALK Break Apart FISH Probe Kit offers a theranostic benefit by being able to identify the very small subgroup of NSCLC patients who would benefit from treatment with Xalkori® (crizotinib), which is an additional treatment option for those with locally advanced or metastatic NSCLC.

The Abbott Vysis ALK Break Apart FISH Probe Kit can quickly identify those who would most benefit from treatment with Xalkori® (crizotinib). In clinical studies, Xalkori® (crizotinib) shrank or slowed tumor growth in the majority of patients.[6]

Time Frames

The assessment should identify time frames that are important in understanding the value of the diagnostic test.

NSCLC can be divided into several stages that describe how far the cancer has spread. Five year survival rates are generally better for those in the earlier stages of lung cancer: [7] [8]

- Stage 0: In this stage, the cancer is limited to the top layers of cells lining the air passages.
- Stage I: In this stage, the tumor is no larger than 5cm in diameter, and has not spread to lymph nodes or distant sites. The five year survival rate for those diagnosed in Stage I is 45-49%.
- Stage II: The cancer has spread to the lymph nodes within the lung and/or the hilar lymph nodes but has not spread to distant sites. In this stage, the five year survival rate is 30%.
- Stage III: In stage III, the cancer can be described as locally advanced. Cancer has spread to the lymph nodes in the middle of the chest and may spread to the lymph nodes on the opposite side of the chest from the tumor. For those diagnosed in Stage III, the five year survival rate is 5-14%.
- Stage IV: At this point, the cancer is advanced and has spread to both lungs and possibly to other parts of the body. At this stage, NSCLC is very hard to treat. When metastatic, the five year survival rate for Stage IV NSCLC is 1%.

Symptoms of lung cancer do not typically become apparent until the cancer is already in a late stage and has spread to other parts of the body. Once the cancer is identified, it is critical to identify and begin the most appropriate treatment for the individual.

Stakeholders

The intended audience for a value assessment affects the framing of the assessment and the drivers and metrics that could be highlighted.

Both the intended audience/stakeholders and the purpose of the assessment should dictate which types of value are considered and emphasized via the assessment process, as well as the types and quality of evidence needed to support evidence development needs and appropriate strategies for collecting annual performance information.

It is important for stakeholders to consider the full range of value drivers and impacts.

The chart on the following page highlights potential value for various stakeholders based on use of the Abbott Vysis ALK Break Apart FISH Probe Kit in screening for ALK-positive NSCLC:

Vysis ALK Break Apart FISH Test Value Drivers Impact by Stakeholder

	Clinical Impact	Non-Clinical Impact	Care Delivery Revenue and Cost Impact	Public/Population Impact
Patient	• Identifies only those who may benefit from Xalkori® (crizotinib) • Highly sensitive in detecting ALK mutation, reducing need for retesting	• Avoids unnecessary side effects for contraindicated patients • May improve chance of survival	• Reduces unnecessary treatment costs by identifying only those who may benefit from Xalkori® (crizotinib)	• Fewer absences from work • Less burden on healthcare resources • May improve chance of survival
Doctor	• Identifies only those who may benefit from Xalkori® (crizotinib) • Highly sensitive in detecting ALK mutation, reducing need for retesting		• Reduces unnecessary treatment costs by identifying only those who may benefit from Xalkori® (crizotinib	• Less burden on healthcare resources • May improve chance of survival
Hospital/Outpatient Clinic			• Reduces unnecessary treatment costs by identifying only those who may benefit from Xalkori® (crizotinib)	• Less burden on healthcare resources
Insurer			• Reduces unnecessary treatment costs by identifying only those who may benefit from Xalkori® (crizotinib)	• Less burden on healthcare resources • May improve chance of survival

Evidence Across the Value Drivers

Diagnostic test innovators must determine the best way to show value with evidence. This can vary based upon the type of test.

It is critical to identify and evaluate the quantity and quality of available types of evidence for the diagnostic test early in product development and on an ongoing basis to determine how it can be used across the relevant drivers to offer robust evidentiary support.

Abbott's evidence focuses on the ALK Break Apart FISH Probe Kit's ability to detect the ALK gene in a small subgroup of NSCLC patients and thus identify them for eligibility for Xalkori® (crizotinib) treatment. Abbott has conducted multiple clinical studies and has engaged in robust sensitivity and specificity analysis.

The chart on the following page applies to the population of patients identified for Crizotinib Treatment following use of ALK Break Apart FISH Testing:

Vysis ALK Break Apart FISH Test Value Drivers by Evidence Source

Evidence	Type of Evidence	Clinical Impact	Non-Clinical Impact	Care Delivery Revenue and Cost Impact	Public/Population Impact
FDA Approval Summary (Published)[9]	Global RCT, Multi-center, Single Arm Study	• Progression-free survival (PFS), the primary endpoint, was significantly longer in the Xalkori® (crizotinib) patients vs. the chemotherapy patients – 7.7 months vs. 3.0 months • Objective response rates (ORRs), a secondary endpoint, substantially increased in Xalkori® (crizotinib) patients – a 46% absolute increase over chemotherapy			• Increased survival rates – trial suggested that survival may be prolonged by Xalkori® (crizotinib) therapy and that receiving Xalkori® (crizotinib) at any time during treatment is beneficial
Expanded Cohort Studying Crizotinib Treatment (Published)[10]	Open-label, Multi-center, Two-part Phase 1 Trial	• Of the 82 patients with FISH-positive ALK rearrangements, there was an overall response rate of 57% to Xalkori® (crizotinib) treatment (vs. ~10% for chemotherapy treatment) and 33% of patients met the criteria for a stable disease rate • The researchers estimated a 6-month probability of progression-free survival of 72% using Xalkori® (crizotinib) (vs. 27.2% using chemotherapy)			
Molecular Analyses of Lung Cancer Patients at the University of Colorado Thoracic Oncology Program (Published)[11]	Retrospective and Prospective Clinical Analysis	• When an average of ~30 tumor cells were used in a FISH assay, specificity was 96.6% and sensitivity was 98.6% • When an average of ~60 tumor cells were used in a FISH assay, specificity and sensitivity were both 100% in determining ALK positively			

Evidence	Type of Evidence	Clinical Impact	Non-Clinical Impact	Care Delivery Revenue and Cost Impact	Public/Population Impact
ALK FISH vs. ALK IHC Competitor Agreement Rates (Published)[12]	Comparative Analysis	• In Trial #1 (aged slides from the original clinical trial), positive percent agreement was 86.0%, negative percent agreement was 96.3%, and overall percent agreement was 94.3% when comparing FISH and a competitor test • In Trial #2 (freshly prepared slide specimens obtained from the original clinical trial patient samples), positive percent agreement was 92.7%, negative percent agreement was 94.8%, and overall percent agreement was 94.1% when comparing FISH and a competitor test			

Expected Impacts (Value)

The value assessment should clearly demonstrate the impact of the diagnostic test across select value drivers including clinical impact, non-clinical patient impact, care delivery revenue and cost impact, and patient/population impact.

These impacts would be offset by the cost of acquiring the technology to derive the total expected value impacts.

Clinical Impact Value – Abbott's ALK Break Apart FISH test provides substantial clinical impact to the patient. Importantly, the test identifies patients for Xalkori® (crizotinib) treatment. When using this treatment, patients saw an increase in progression-free survival (PFS), objective response rates (ORRs), and disease stability. The 6-month probability of progression-free survival, for example, was estimated at 72% when using Xalkori® (crizotinib), which is a significant increase compared to 27.2% when using chemotherapy.[13] Finally, the test is highly sensitive and specific and established the clinical performance standard against which competitor tests concordance was evaluated.[14]

Non-Clinical Impact Value – The ALK Break Apart FISH test also provides non-clinical benefits to patients and other stakeholders. Using FISH to identify patients for Xalkori® (crizotinib) therapy led to tumor shrinkage and disease stability in most patients.[15] The patient experience is enhanced because they have an increased chance of survival compared to traditional chemotherapy treatments. This may lead to a quicker return to work and daily activities and a lessened burden on caregivers.

Care Delivery Revenue and Cost Impact Value – The ALK Break Apart FISH test also delivers economic impacts. Since diagnostic companion testing can lead to more accurate and precise results, unnecessary treatments, and the costs associated with those treatments, can be avoided. This ultimately leads to decreased downstream utilization and cost savings.

Public/Population Impact Value – The ALK Break Apart FISH test creates beneficial societal impacts by potentially increasing survival rates for NSCLC patients, further highlighting the importance of prospective genotyping in certain patient populations. Increased survival rates can result in fewer absences from work, increased productivity, and a reduced strain on health care resources.

[1] “A Framework for Comprehensive Assessment of the Value of Diagnostic Tests”, co-developed with Deloitte Consulting LLP, available at www.advamed.org and co-developed with Deloitte Consulting LLP
[2] "Key Statistics for Lung Cancer." American Cancer Society.
[3] "Targeted Therapy Drugs for Non-Small Cell Lung Cancer." American Cancer Society.
[4] Ibid.
[5] "Non-Small Cell Lung Cancer Stages." American Cancer Society.
[6] Kazandjian et al. “FDA Approval Summary: Crizotinib for the Treatment of Metastatic Non-Small Cell Lung Cancer With Anaplastic Lymphoma Kinase Rearrangements.” The Oncologist 19.10 (2014): 5–11.
[7] "Non-Small Cell Lung Cancer Survival Rates, by Stage." American Cancer Society.
[8] "How XALKORI® (crizotinib) Works." XALKORI® (crizotinib).
[9] Kazandjian et al. “FDA Approval Summary: Crizotinib for the Treatment of Metastatic Non-Small Cell Lung Cancer With Anaplastic Lymphoma Kinase Rearrangements.” The Oncologist 19.10 (2014): 5–11..
[10] Kwak et al. “Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer.” The New England Journal of Medicine 363.18 (2010): 1693-1703.
[11] Camidge et al. “Optimizing the Detection of Lung Cancer Patients Harboring Anaplastic Lymphoma Kinase (ALK) Gene Rearrangements Potentially Suitable for ALK Inhibitor Treatment.” Clinical Cancer Research 16.22 (2010): 5581–5590.
[12] “VENTANA ALK (D5F3) CDx Assay.” Ventana Product Document Library. Ventana Medical Systems, Inc. 2016.
[13] Kwak et al. “Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer.” The New England Journal of Medicine 363.18 (2010): 1693-1703.
[14] Ibid.

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Abbott: Vysis ALK Break Apart FISH Probe Kit Test

Lung cancer is divided into two main categories – non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). About 5% of individuals with NSCLC have a genetic mutation involving the ALK (anaplastic lymphoma kinase) gene that allow cells to grow and spread uncontrollably. The ALK protein can be targeted by certain drugs that can be used after chemotherapy has stopped working or instead of chemotherapy. Xalkori® (crizotinib) is an oral receptor tyrosine kinase inhibitor indicated for use in patients with locally advanced or metastatic NSCLC that is ALK-positive.

Patient Needs

New Dx Test/ Technology

Stakeholders

Patient | Physician | Hospital | Clinical Labs | Payer | Government | Employer

Stakeholders

Value Drivers

- **Clinical Impact**
  - Highly sensitive in detecting ALK mutation
  - Identified only those who may benefit from crizotinib
- **Non-Clinical Patient Impact**
  - Avoids unnecessary side effects for contraindicated patients
  - May improve chance of survival

Test Type

Value Drivers

- **Care Delivery Revenue and Cost Impact**
  - Reduces unnecessary treatment costs by only identifying patients who may benefit from crizotinib
- **Public/ Population Impact**
  - Less missed work
  - Reduced burden on healthcare resources
  - May improve chance of survival

Patient Populations

- Patients with locally advanced or metastatic ALK-positive NSCLC who may benefit from treatment with crizotinib

Evidentiary Support

- FDA Approval Summary
- Expanded Cohort Studying Crizotinib Treatment
- Molecular Analyses of Lung Cancer Patients at Univ. of CO Thoracic Oncology Program
- ALK FISH v. ALK IHC Competitor Agreement Rates

Time Frames

- Determining crizotinib effectiveness in Stage 0-IV NSCLC patients

Expected Impacts (Value)

- Identifies only patients who will benefit from crizotinib treatment
- High sensitivity in detecting ALK mutation
- Avoids unnecessary side effects
- May improve chance of survival
- Reduces unnecessary treatment costs
- Reduces absences from work
- Reduces burden on healthcare resources

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