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June 16, 2016

On behalf of Boehringer Ingelheim Pharmaceuticals Inc., I am writing to follow up on a May 16th meeting with Dr. Robert Carlson, Dr. Marian Birkeland and Ms. Joan McClure on the impact of delays in time to biomarker test result in regard to the care of patients with advanced NSCLC.

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Specific Change: We respectfully request that the NCCN Non-small Cell Lung Cancer (NSCLC) panel consider inclusion of language in the advanced NSCLC Guidelines that would provide clear expectation regarding minimizing the time from biopsy/tissue procurement to result availability. Minimizing this time will address a significant gap in care in terms of accurate diagnosis and appropriate use of targeted therapies.

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Rationale: Current language in other guidelines (CAP/IASLC/AMP) are accommodating to delays in the hospital setting (Medicare 14 Day Rule), and state that "EGFR and ALK results should be available within 2 weeks (10 working days) of receiving the specimen in the testing laboratory" (1). Arguably, this language could be more specific and provide clearer expectation around the time from biopsy to laboratory and result in hand that would help to eliminate delays to test result for physicians and patients.

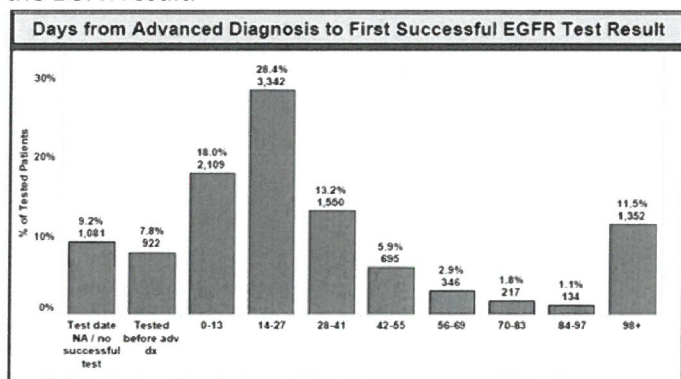
A growing body of evidence demonstrates a clear impact on treatment selection for patients with advanced NSCLC. In an NCCN Trends Survey completed by BI in October 2014, it was found that:

- 69% of US-based responders (n=169) would wait no more than one week for mutation status results before initiating therapy in the first line setting.
- In the absence of a biomarker result (EGFR) due to inadequate tissue, 65% would rebiopsy and initiate chemo before potentially switching to a TKI. Half of these would complete the 4-6 cycles of chemotherapy before making the switch, regardless of timing of result.
- Fully two-thirds of the time, results took more than two weeks to obtain (with less than two weeks being cited as the optimal time to result).

Based on a 2016 estimate of 224,390 new cases of lung cancer and rates of referral to oncologists, (2)(), as well as biomarker test statistics, (3), an estimated 81,686 (36%) patients did not have had biomarker results at their first oncology visit. Of

these, 11,039 patients did not have sufficient tissue for analysis from the diagnostic biopsy, and 27,045 patients did not undergo biomarker testing at all. For patients without biomarker results at first oncology visit, median time from first oncology appointment to biomarker results availability was 21 days when testing was carried out.

Additional data from Flatiron suggests 28.4% of the time, patients and physicians are waiting between 14-27 days from advanced diagnosis to first successful EGFR test result, while 36.4% of the time, patients are waiting more than one month for the EGFR result.



Source: Flatiron NSCLC Dashboard, reported March 2016 (Jan. 2011-Mar. 2016). n=23,733 patients

Cited reasons for potential delays include:

- Unsuccessful first biopsy attempt/QNS (12-20% of the time, varies by source) result at time of first oncology visit.
- Further need for biomarker testing education
- Medicare 14 Day Rule Impact

In their 2016 “Hope Summit Patient Survey,” Lungevity reports that just over a third of patients were started on a treatment therapy before knowing the results of their biomarker test. Time to result is critical—published information in NSCLC provides evidence that treatment delay can lead to progressed disease, and makes the statement that efforts to diagnose, stage and begin treatment should be done in an expedited fashion, with complete restaging, etc. strongly recommended after delays of 4-8 weeks (4). Not having a timely result in hand to guide appropriate therapeutic intervention can often result in chemotherapy or no therapy at all in the front line or subsequent lines of advanced EGFRm+ NSCLC when patients and physicians feel the need to start treatment in the absence of molecular testing results. In the era of targeted therapies, this is unacceptable.

References:

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with advanced nonsmall-cell lung cancer. *Annals of Oncol*. (2015): mdv208
4. Nasiruddin M, et al. Rapid Disease Progression With Delay in Treatment of
Non-Small-Cell Lung Cancer. *Int J of Rad Oncol* Biol* Physics* 79, no. 2
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Sincerely,



William F. Goeckeler, Ph.D.

Attachment: Background information on: Medicare's "Laboratory Date of Service for Specimens" regulation (DOS Rule) on precision medicine diagnostics.

History: Medicare 14 Day Rule Impact

Medicare's "Laboratory Date of Service for Specimens" regulation (DOS Rule) on precision medicine diagnostics.

As discussed in the attached letter, the DOS rule continues to limit beneficiary access and create inconsistent coverage determinations for advanced diagnostics that are offered by a single laboratory and not commonly performed by hospital laboratories. The DOS Rule, in combination with the separate hospital bundling rules, requires hospitals to bill in certain cases for tests that are performed at an independent laboratory following the patient's hospital encounter. These billing rules create significant administrative challenges for laboratories, hospitals, physicians, and patients and have limited access to these advanced diagnostic tests.

I. Background on the Date of Service

The date of service is a required data field for claims submission for clinical laboratory diagnostic tests. Prior to 2001, the billing rules considered a variety of time periods including the date of specimen collection, date of physician ordering, the date the laboratory accesses the specimen and the date of performance of the test to be the date of service. As part of the negotiated rulemaking in 2001 for clinical diagnostic laboratory tests, CMS established a uniform Date of Service standard in regulation for all clinical laboratory tests. While the final rule was a negotiated rulemaking, there was no consensus among the laboratory industry on the appropriate standard for the date of service. In the final rule, Medicare established the date of service as the "date of specimen collection".

It is important to note that when establishing the DOS Rule, CMS conceived of the DOS Rule as intended to promote "program integrity and national uniformity, yet minimize the burden on laboratories." However, entirely separate Medicare regulations provide that a hospital must bill Medicare directly for services furnished when the patient was in or at the hospital (commonly referred to as the "Hospital Bundling Rule"). This rule applies to all hospital services, not just clinical diagnostic laboratory tests. As a result of the DOS Rule's interaction with the hospital bundling rule, when a laboratory test's "date of service" falls within a hospital visit, the hospital -- not the laboratory that performs the test -- must bill Medicare for the service.

CMS modified the DOS Rule in the 2007 Physician Fee Schedule Final Rule to create specialized rules for clinical tests laboratory tests performed on stored or archived specimens. The agency sought to distinguish those tests that "would almost never affect the treatment regimen at the hospital" from those tests "directly related to not only the condition for which the patient is hospitalized, but would typically be used for specific care during the hospital stay as well, if available during the hospital stay." As a result of the 2007 modifications, for certain tests performed

on stored specimens at least 14 days after a patient's discharge from a hospital, the date of service is now the date that the test was performed.

In 2010, Congress passed legislation to require CMS to run a two year demonstration project to examine the impact of the DOS rule on complex diagnostic laboratory tests. Congress recognized that the current DOS rule creates barriers and administrative complexities for hospitals and physicians to order complex diagnostic laboratory tests performed by independent laboratories. A primary goal of the Demonstration was to increase access to tests within 14 days of discharge from a hospital by allowing the independent laboratory to bill for the test rather than bundling into hospital payment. The Final Report on the demonstration project was released by CMS in January, 2016, and does not include any policy recommendations.

II. DOS Rule Creates Inconsistent Coverage Policies and Limits Beneficiary Access to Advanced Diagnostic Tests

Advanced diagnostics are proprietary assays performed by a single laboratory. These types of tests have a different pattern of clinical use that makes them less tied to a primary service in the hospital outpatient setting than the more common and routine laboratory tests. In many instances, advanced diagnostic tests are ordered by a physician as part of an office visit. Often times, these physicians' offices are affiliated with hospitals so the physician will direct the patient to a hospital-affiliated laboratory to collect the sample. The sample is then sent to the independent laboratory to conduct the proprietary test and the test results are sent directly to the physician. The patient is only in the hospital outpatient setting because their physician is affiliated with the hospital, not because the care is tied to a hospital service. In this situation, the test is billed as a hospital service only as an administrative matter resulting from the DOS rule.

The impact of the DOS rule has become more wide spread in recent years as more physician practices have been consolidated and acquired by hospitals. There was "significant increases in consolidation between outpatient oncology practices and hospitals and/or health systems (vertical consolidation) in local markets between 2003 and 2013." Advanced diagnostics that previously would have been billed to Medicare by the independent lab are now pulled into the DOS Rule and the hospital must bill for the test. Hospitals do not want to bill for tests that they do not perform and assume the financial risk of that service. As a result, some hospitals are delaying or forgoing testing for certain Medicare patients.

The DOS Rule leads to multiple different billing scenarios depending on where the specimen is collected, when the test is ordered, and what insurance program the patient is enrolled in. These different billing scenarios impact which patients receive advanced diagnostic testing. It is important to note that Medicare Advantage plans and private payers generally require the laboratory that performed the test to bill for the test regardless of where the specimen is collected. Within the Medicare Fee For Service program the DOS Rule creates inconsistent coverage policies. The DOS Rule can result in different coverage decisions

depending on when a test is ordered and where the hospital is located. Laboratory tests are typically billed to the Medicare contractor in the region where the laboratory is located. These local contractors in effect establish a national coverage policy for a particular test performed in its jurisdiction. However, under the DOS rule a hospital may be required to bill a MAC located in a separate jurisdiction from where the test is performed. As coverage policies in the hospital and laboratory's MAC regions may vary, the same test may be covered if it is ordered 15 days after specimen collection but not if it is ordered 13 days after collection.

For example, many of these advanced diagnostic tests are covered under the MoIDX Program which currently applies in four MAC regions totaling 26 states. For covered-tests performed by a laboratory in the MoIDX region, but ordered by a hospital outside of the MoIDX region, the test would not be covered if it is ordered within 14 days of the patient visit. That same test, however, would be covered if the blood draw was collected outside of the hospital.