

## Health Industry Alert

March 22, 2018

### Key Points

- The new national Medicare coverage determination covers only FDA-authorized NGS tests with companion diagnostic indications, leaving NGS cancer tests without that specific indication to seek coverage from local Medicare contractors.
- This final NCD complements FDA's evolving approach to facilitating, rather than mandating, the submission of LDTs for FDA review.
- NGS tests may be eligible for a distinct Medicare payment status, but the terms of this payment status may prevent laboratories from licensing their tests.



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## New CMS National Coverage Determination and FDA Regulatory Approach: the Next Generation for NGS Testing Policy?

### Intro

On March 16, 2018, the Centers for Medicare and Medicaid Services (CMS) finalized a national coverage determination (NCD) for next-generation sequencing (NGS) tests for cancer, marking a significant step in the evolution toward personalized medicine. Using NGS to help assess cancer treatments allows clinicians to test cancerous samples to identify all genomic alterations that drive solid tumor growth at once, as opposed to traditional assays for one mutation at a time. NGS presents numerous questions—relating to Medicare coverage, coding, reimbursement and marketing authorization from the Food and Drug Administration (FDA). Both CMS and the FDA have now announced new approaches regarding NGS-related issues. This final NCD highlights that their frameworks may not be perfectly aligned.

The final NCD policy, like the proposed decision, strongly favors tests approved or cleared by FDA—making FDA marketing authorization a precondition to obtaining Medicare coverage at the national level. Specifically, this NCD limits national coverage to those FDA-approved or -cleared tests with **companion diagnostic** indications, meaning that tests are authorized to provide information that is essential to the safety and effective use of a specific therapy, often by determining patient eligibility for the therapy. The final policy eliminates the proposed path to national coverage for cleared tests without companion diagnostic indications through coverage with evidence development (CED). Unlike the draft decision, however, tests without any FDA marketing authorization may still seek coverage through their local Medicare administrative contractors (MACs).

Although CMS changed the final policy to provide national coverage for FDA-cleared companion diagnostics (as opposed to only FDA-**approved** companion diagnostics), FDA has never authorized a companion diagnostic that uses NGS through the moderate-risk, clearance pathway. This policy comes after FDA recently granted approval, the more rigorous standard for higher-risk devices, to four companion diagnostics, clearance to one NGS test without a companion diagnostic indication and clearance to one companion diagnostic that does not use NGS. FDA also recently announced a streamlined regulatory approach to reporting biomarkers for NGS tests. In the wake of CMS's recent decision, laboratory test developers will need to determine whether to pursue either initial or broadened FDA authorization, and how to frame their indications for use to facilitate national coverage.

In parallel to CMS, FDA's recent actions indicate a sea change, as some of these tests qualify as laboratory-developed tests (LDTs). LDTs are tests developed by a single lab certified under Clinical Laboratory Improvement Amendments (CLIA), and have historically been subject to enforcement discretion. In recent years, however, FDA has expressed intent to regulate LDTs as medical devices, although the agency never finalized a draft guidance issued in 2014 that would have mandated premarket authorization for certain LDTs.

Even with FDA authorization and Medicare coverage, however, laboratories must still determine coding and reimbursement, which depend, in part, on CMS's lagging implementation of a new regulatory pathway to reimburse for laboratory tests under the Protecting Access to Medicare Act of 2014 (PAMA). This alert explores these recent developments and identifies key decision points for test developers.

## **CMS Final NCD for NGS Tests for Cancer**

Until now, coverage of NGS tests was set by local coverage policies of Medicare contractors. Some contractors covered these tests under local coverage determinations or on a case-by-case basis. In some regions, however, these tests were not covered at all. Based on the final NCD, this will likely remain the case for most NGS-based tests for cancer, unless they are FDA-approved companion diagnostics.

On November 30, 2017, CMS announced a proposed NCD for NGS cancer tests that would have supplanted these local coverage decisions.<sup>1</sup> The draft policy proposed national coverage for only FDA-approved companion in vitro diagnostics for patients with recurrent, metastatic or advanced stage IV cancer. CMS also proposed CED requirements for FDA-approved or -cleared tests (participation in the NIH Genetic Testing Registry), and tests without any marketing authorization (participation in an NIH-NCI National Clinical Trial Network clinical trial and the NIH Genetic Testing Registry). Critically, the draft would have established a policy of **non-coverage** of NGS as a diagnostic laboratory test when the patients did not have noted indications or the test did not meet the coverage or CED criteria.

The final NCD differs from the draft in several key respects:

- expands coverage from patients with recurrent, metastatic or advanced stage IV cancer to those with either "recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer"

- permits repeat testing using the same NGS test when a new primary cancer diagnosis is made by the treating physician
- provides national coverage for FDA-cleared companion in vitro diagnostics, in addition to FDA-approved companion in vitro diagnostics
- eliminates the CED option
- reverses the proposed policy of non-coverage and allows local Medicare contractors to cover NGS at their discretion when patients meet certain conditions.

CMS also clarified that the NCD applies to only the use of diagnostic laboratory tests for beneficiaries with cancer and that coverage of NGS testing for other conditions is left to the local MACs.

The final NCD is broader than the draft in that it now covers FDA-cleared tests whereas, previously, only FDA-approved tests were eligible for coverage without any CED requirements. However, national coverage still applies to only tests with companion diagnostic indications; as of yet, there are no FDA-cleared NGS tests with companion diagnostic indications. The policy is narrower in that FDA-cleared tests without such companion diagnostic indications now do not have the option of pursuing national coverage by complying with the CED requirements, they only have the opportunity to seek local coverage through their MAC, and MACs continue to have the discretion to deny coverage.

## **FDA Marketing Authorization**

As noted above, the CMS coverage policy strongly favors tests with FDA marketing authorization. Unlike the draft, however, the final coverage policy still permits makers of LDTs to pursue coverage with their local MACs.

- *Background on LDTs*

FDA has previously defined an LDT as an in vitro device that is intended for clinical use and designed, manufactured, and used within a single laboratory.<sup>2</sup> FDA has generally asserted jurisdiction over LDTs, and it even issued draft guidance proposing to apply device regulatory requirements to some LDTs, but they have remained under enforcement discretion.<sup>3</sup> In particular, while some LDT sponsors have sought marketing authorization from FDA, FDA has not required LDTs to obtain clearance or approval.

Several legislative proposals under consideration by Congress would create a separate regulatory paradigm for in vitro diagnostics, including LDTs. For example, a discussion draft of the Diagnostic Accuracy and Innovation Act, released in March 2017, would establish a risk-based classification system for in vitro clinical tests, require FDA approval for high-risk tests and create a new FDA center to regulate tests.<sup>4</sup> The post-market obligations under this paradigm would resemble those for in vitro diagnostics with more limited adverse event reporting (compared to medical devices), eliminate the overlap between CMS and FDA oversight, and create a new user fee program. FDA Commissioner Scott Gottlieb has expressed his support for a comprehensive legislative approach to LDTs.<sup>5</sup>

- *Recent Developments in the Regulation of NGS Tests*

Despite the lack of certainty surrounding FDA's regulation of LDTs, FDA has moved forward with its efforts to support precision medicine, and NGS technology in particular. In the summer of 2016, Foundation Medicine entered FDA/CMS Parallel Review, a program through which the two agencies coordinate with sponsors as they work to obtain FDA marketing authorization and Medicare coverage at the same time. Over the course of 2017, FDA approved several NGS tests with companion diagnostic claims through the Premarket Application (PMA) pathway for higher-risk Class III devices, including Thermo Fisher Scientific's OncoPrint™ Dx Target Test, Illumina's Praxis™ Extended RAS Panel, and Foundation Medicine's Foundation Focus™ CDxBRCA and F1CDx. In addition, FDA announced that Memorial Sloan Kettering Cancer Center received de novo clearance for its MSK-IMPACT NGS test as a moderate-risk Class II device. Shortly thereafter, FDA released a new policy for tumor-profiling NGS tests in keeping with its movement toward a more "fluid" approach to digital health regulation. The policy outlines a three-tiered approach for reporting biomarkers in NGS tests:

- Level 1: Companion Diagnostics:
  - Tests making companion diagnostic claims that are prescriptive for a specific product (i.e., naming a corresponding drug) must be supported by clinical outcomes data.
- Level 2: Cancer Mutations with Evidence of Clinical Significance:
  - Tests that report biomarkers described as cancer mutations with evidence of clinical significance must be supported by a demonstration of analytical validity and clinical validity.
- Level 3: Cancer Mutations with Potential Clinical Significance:
  - Tests that report cancer mutations that do not meet Level 1 or 2 must be supported by analytical validation and clinical or mechanistic rationale for inclusion in the panel.
  - They may be informational or used to direct patients toward clinical trials.
  - Mutations may move from Level 3 to Level 2 without additional FDA clearance (with sufficient evidence).<sup>6</sup>

In addition, FDA certified the New York State Department of Health (NYSDOH) as a third-party reviewer, such that NYSDOH can review a test submission and recommend it to FDA for clearance (i.e., Level 2 tests).<sup>7</sup>

In light of FDA's new approach to NGS tests, it was unclear whether FDA and NYSDOH would have had the capacity to review the substantial volume of submissions that might have resulted from the draft NCD. Because the draft policy effectively excluded tests without FDA authorization, and LDTs, up until now, have largely been subject to enforcement discretion, many sponsors of LDTs may have been persuaded to seek FDA authorization for their NGS tests. The volume of submissions may still present a concern under the final policy, depending, in part, on how local MACs react to requests for coverage, and how FDA approaches submissions relating to companion diagnostic indications.

To secure national coverage, though, developers would need to obtain FDA marketing authorization with a companion diagnostic indication; some may still decide that it is worthwhile, given the potentially disparate coverage policies likely to result from local MACs. During a recent speech before the American Clinical Laboratory Association (ACLA), Commissioner Gottlieb indicated that FDA is developing several policies designed to improve the development and review of NGS technologies, including final guidance on FDA's "broader and more flexible regulatory approach to all NGS tests."<sup>8</sup> These policies may make it easier to obtain these marketing authorizations, or at least make the expectations more clear.

### **Medicare Reimbursement<sup>9</sup>**

NGS tests covered under this policy are potentially eligible for a distinct Medicare payment status created under PAMA.<sup>10</sup> However, CMS has yet to implement PAMA fully, despite the provisions relating to payment for laboratory tests taking effect on January 1, 2018. In addition, the conditions for receiving this payment may or may not be worthwhile for laboratories, as discussed further below.

PAMA created a new category of tests known as "Advanced Diagnostic Laboratory Tests" (ADLT), a subset of which, "new ADLTs," will receive payment based on the actual list charge for an initial period of three quarters of the time that the test is on the market, known as the "initial period."<sup>11</sup> If it is later determined that the list price exceeds payments received by private payers by more than 130 percent, CMS is permitted to claw back the difference. PAMA defines an ADLT as a clinical diagnostic laboratory test that is:

- covered under Medicare Part B
- offered and furnished by only a single laboratory
- not sold for use by a laboratory other than the original developing laboratory (or a successor owner) and
- meets **one** of the following criteria:
  - The test is an analysis of multiple biomarkers of DNA, RNA, or proteins combined with a unique algorithm to yield a single patient-specific result.
  - The test is cleared or approved by the FDA. **or**
  - The test meets other similar criteria established by the Secretary.<sup>12</sup>

A "new" ADLT is one for which payment has not been made under the Clinical Laboratory Fee Schedule (CLFS) prior to January 1, 2018.<sup>13</sup>

NGS tests are likely eligible to be considered ADLTs, either through obtaining FDA clearance or approval, or by virtue of meeting the criteria for a biomarker test. Even if the test meets the defined criteria, though, there is some ambiguity as to whether certain laboratories are eligible to receive this payment status for the initial period. Under PAMA, laboratories that meet the definition of an "applicable laboratory" are required to report private payer rates to CMS, upon which CMS will determine payment based on the weighted median private payer rate for that test.<sup>14</sup> Reporting is not voluntary (i.e., nonapplicable

laboratories may not report to CMS).<sup>15</sup> Instead, they will continue to be reimbursed based on the methods in place now: crosswalking or gapfilling.<sup>16</sup> Although PAMA requires applicable laboratories that develop new ADLTs to report private payer rates at the end of the second quarter,<sup>17</sup> neither PAMA, nor the implementing regulations or guidance explicitly require such laboratories to be “applicable laboratories” to receive the special payment status. In fact, the final rule implementing PAMA provides that, if the entity does not have private payer rates to report at that time, the entity will be paid based on a different methodology until it does, further indicating that laboratories do not need to be applicable laboratories to receive list price for the initial period.<sup>18</sup> After all, the initial list price is not dependent on a CMS calculation of private payer rates.

This is important because most hospital laboratories, many of which develop NGS tests, are unlikely to meet the definition of an applicable laboratory. Applicable laboratories must earn more than 50 percent of their revenue from the Physician Fee Schedule or CLFS and the majority of hospital laboratories will not meet that threshold because they must report at the hospital National Provider Identifier level, instead of the narrower laboratory level.<sup>19</sup> Indeed, ACLA is suing CMS on the basis that CMS illegally exempted hospitals from reporting private payer rates, thereby skewing the weighted median private payer rates.<sup>20</sup>

Regardless of whether laboratories are eligible to receive the list price for the initial period, laboratories may determine that meeting the criteria for an ADLT is not the most attractive reimbursement option because it may prevent the laboratories from licensing the test. This is because ADLTs must be “offered and furnished only by a single laboratory” and “not sold for use by a laboratory other than the original developing laboratory (or a successor owner).”<sup>21</sup> In the preamble to the final rule implementing PAMA, CMS reasoned that “the statute intends for special payment status to be awarded to the one laboratory that is expending the resources for all aspects of the test. . . . The laboratory that markets and performs the test must also be the only one to sell it, that is, to receive remuneration in exchange for performing the test.”<sup>22</sup> CMS also clarified that an FDA-cleared or -approved test that is sold to multiple labs as a kit for “off-the-shelf” use would not qualify for ADLT status because it is offered and furnished by more than one single laboratory.<sup>23</sup> Therefore, to the extent that a licensing arrangement would allow other laboratories to perform the test, the test would not be considered an ADLT.

In addition, according to CMS, a test is not an ADLT in the situation where a laboratory purchases/obtains licensing rights to intellectual property for a test and then develops it for commercialization because the laboratory “would not be expending its own resources on all aspects of the development of the test. . . .”<sup>24</sup> To be clear, a laboratory could still receive reimbursement for a new ADLT if it receives referrals from other entities and performs the test itself.<sup>25</sup> It may be less clear, however, whether the test may still be considered an ADLT if the laboratory receives patient samples from other institutions or laboratories. On the one hand, if the process for obtaining the sample is considered a part of the “test,” that initial aspect would need to be performed at the single laboratory. However, even though patient sample collection may be described as part of the test, it is possible that certain validating controls would take place at the laboratory, and CMS would find that such a test could still be an ADLT.

As a result, test developers should carefully evaluate whether obtaining the list price for the initial period is favorable to licensing their tests from a reimbursement perspective. CMS has stated that the ADLT application and guidance are forthcoming.

### **Medicare Coding**

PAMA also made changes to the coding process for laboratories, and ADLTs specifically, which may impact reimbursement. PAMA provides that FDA-cleared or -approved tests must obtain a unique billing code and that CMS will adopt unique codes for ADLTs.<sup>26</sup> For clinical diagnostic laboratory tests (CDLTs) that are not ADLTs, more than one laboratory will use the same code for the test. As noted above, CMS will determine payment rates based on the weighted median private payer rate for “applicable laboratories,” meaning that the rates that other laboratories secure from private payers will influence the Medicare payment amount for all applicable laboratories using that code.

Reimbursement for ADLTs that are not furnished by applicable laboratories may also be affected by this reporting construct. Recall that CDLTs, including ADLTs, that are not furnished by applicable laboratories will continue to be priced based on crosswalking or gapfilling. As part of the CMS annual laboratory meeting, laboratories typically request that CMS either assign a payment rate based on the payment rate of a test with similar technological capabilities and value that is already on the CLFS (i.e., “crosswalk” the new test to an existing test) or gapfill the test. Therefore, new tests that crosswalk to tests with payment rates that reflect the weighted median private payer rate will also reflect those market rates. Through the gapfilling process, on the other hand, the laboratory must work with its local MAC to determine the payment amount based on a variety of factors, which typically offers less certainty from the laboratory’s perspective. Although CMS has not issued formal guidance implementing the coding aspects of PAMA, test developers must determine whether to seek Proprietary Laboratory Analysis billing codes from the American Medical Association or request Healthcare Common Procedure Coding System codes from CMS, which are issued at different intervals. Laboratories, including hospital laboratories, must evaluate these timing variables, the most efficient way to obtain a new code, and how these coding options may affect patient access and reimbursement in the short and long term.

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- <sup>1</sup> CMS, Proposed Decision Memo for Next Generation Sequencing for Medicare Beneficiaries with Advanced Cancer (CAG-00450N), *available at* <https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=290&TimeFrame=7&DocType=All&bc=AAAAIAAAQAAA&>.
  - <sup>2</sup> FDA, Draft Guidance, Framework for Regulatory Oversight of Laboratory Developed Tests 5 (Oct. 3, 2014), *available at* <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf> [hereinafter, “FDA Draft LDT Guidance”].
  - <sup>3</sup> *Id.* CMS has been charged with regulating the accreditation, inspection and certification process for laboratories that make LDTs under CLIA since 1988, and there has long been a question of whether FDA has the authority to regulate tests developed and administered by CLIA laboratories. Given the growing sophistication of LDTs over time, FDA released draft guidance in October 2014 that would have subjected certain LDTs to premarket review, Quality Systems requirements, medical device reporting, and registration and listing requirements. The framework would have employed a risk-based approach that would have been phased in over time and would have grandfathered certain tests. *Id.* at 7–29. However, the Obama administration never released final guidance, and FDA has signaled that its proposed approach to LDTs is now inoperative. In early 2017, FDA announced that it would not issue final guidance on LDTs at that time to allow for further public discussion on an appropriate oversight approach, recognizing the need for continued evaluation. FDA, Discussion Paper on Laboratory Developed Tests (Jan. 13, 2017), *available at* <https://www.fda.gov/downloads/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/laboratorydevelopedtests/ucm536965.pdf>.
  - <sup>4</sup> Diagnostic Accuracy and Innovation Act (Discussion Draft, March 2017), *available at* <https://bucshon.house.gov/sites/bucshon.house.gov/files/documents/daia%20discussion%20draft.pdf>.
  - <sup>5</sup> Beth Wang, Inside Health Policy, *Gottlieb: Congress Should Regulate LDTs, LDT Community Should Rethink Marketing* (Sept. 18, 2017), <https://insidehealthpolicy.com/daily-news/gottlieb-congress-should-regulate-ldts-ldt-community-should-rethink-marketing>.
  - <sup>6</sup> FDA, Fact Sheet: CDRH’s Approach to Tumor Profiling Next Generation Sequencing Tests (Nov. 15, 2017), <https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM584603.pdf>.
  - <sup>7</sup> FDA, Press Release, FDA Unveils a Streamlined Path for the Authorization of Tumor Profiling Tests Alongside its Latest Product Action (Nov. 15, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585347.htm>; FDA, Current List of Accredited Persons for 510(k) Review under the FDA Modernization Act of 1997 (last updated March 19, 2018), [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/Accredit.CFM?party\\_key=9](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/Accredit.CFM?party_key=9).



<sup>8</sup> Scott Gottlieb, Comm'r, FDA, Remarks at the American Clinical Laboratory Association Annual Meeting (March 6, 2018), *available at* <https://www.fda.gov/NewsEvents/Speeches/ucm599551.htm>.

<sup>9</sup> This alert focuses on only Medicare reimbursement, not reimbursement by commercial payers or Medicaid.

<sup>10</sup> See *generally*, Protecting Access to Medicare Act of 2014, Pub. L. No. 113-93.

<sup>11</sup> 42 U.S.C. § 1395m-1(d).

<sup>12</sup> 42 U.S.C. § 1395m-1(d)(5).; CMS-1621-F, Medicare Clinical Diagnostic Laboratory Tests Payment System Final Rule, Frequently Asked Questions Q&A 6.2 (last updated March 9, 2017), *available at* <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Downloads/CMS-1621-F-FAQ.pdf> [hereinafter, "CMS PAMA FAQ"].

<sup>13</sup> 42 U.S.C. § 1395m-1(d)(1)(A) 42 C.F.R. § 414.502.

<sup>14</sup> 42 U.S.C. § 1395m-1(a).

<sup>15</sup> *Id.*; CMS PAMA FAQ, at Q&A 2.7.

<sup>16</sup> CMS PAMA FAQ, at Q&A 1.7.

<sup>17</sup> 42 U.S.C. § 1395m-1(d)(2); CMS, Medicare Program; Medicare Clinical Diagnostic Laboratory Tests Payment System; Final Rule, 81 Fed. Reg. 41,036, 41,065 (June 23, 2016).

<sup>18</sup> 81 Fed. Reg. at 41,068.

<sup>19</sup> CMS PAMA FAQ, at Q&A 2.8, Q&A 2.11, Q&A 2.17.

<sup>20</sup> Complaint, Am. Clinical Laboratory Ass'n v. Hargan, No. 1:17-cv-02645 ( D.D.C. Dec. 11, 2017), *available at* <http://www.acla.com/wp-content/uploads/2017/12/ACLA-PAMA-Complaint.pdf>.

<sup>21</sup> 42 U.S.C. § 1395m-1(d)(5).

<sup>22</sup> 81 Fed. Reg. at 41,056.

<sup>23</sup> *Id.* at 41,061.

<sup>24</sup> *Id.* at 41,060.

<sup>25</sup> *Id.* at 41,056.

<sup>26</sup> 42 U.S.C. § 1395m-1(e).