September 7, 2023

VIA Electronic Mail to: ProposedLCDComments@novitas-solutions.com

Novitas Solutions
Medical Affairs
Suite 100
2020 Technology Parkway
Mechanicsburg, PA 17050

RE: Proposed LCD – Genetic Testing for Oncology (DL39365)

Dear Dr. Mann:

On behalf of the Coalition for 21st Century Medicine (C21), thank you for the opportunity to submit comments regarding the above-captioned proposed local coverage determination (LCD). C21 comprises many of the world's most innovative diagnostic technology companies, clinical laboratories, physicians, venture capital companies, and patient advocacy groups. C21's mission is to improve the quality of health care by encouraging research, development, and commercialization of innovative diagnostic technologies that will personalize patient care, improve patient outcomes, and substantially reduce health care costs.

For the reasons outlined below, C21 respectfully recommends that Novitas withdraw the draft LCD at the end of the comment period, and convene one or more Contractor Advisory Committee (CAC) meetings before engaging in future LCD development in genetic testing for oncology – both with respect to such tests in general, as well as the 13 specific tests evaluated in the proposed LCD. Engagement with the CAC would allow Novitas to obtain input from healthcare professionals, beneficiary representatives, and representatives of medical organizations to obtain meaningful feedback that would "ensure an unbiased and contemporary consideration of 'state of the art' technology and science" and would support the development of a clinically appropriate LCD.[1] By considering the CAC's input (as well as that from interested stakeholders, like C21), Novitas could address key clinical questions and develop an updated proposal to ensure that Medicare beneficiaries will continue to have timely access to advanced molecular diagnostic tests.

Alternatively, if Novitas elects to finalize the LCD, C21 recommends that Novitas modify the LCD to remove the presumption against coverage for tests not supported in at least one of the three listed compendia, and convene a CAC meeting before finalizing non-coverage for the 13 specifically-referenced tests.

[1] Medicare Program Integrity Manual ch. 13, § 13.2.4.3.

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1. SUPPORT FOR NOVITAS'S LONGSTANDING APPROACH TO COVERAGE OF DIAGNOSTIC TESTING SERVICES

For more than sixteen years, C21 has worked with the Centers for Medicare & Medicaid Services (CMS) and Medicare Administrative Contractors (MACs) on the development, promulgation, and implementation of policies intended to facilitate appropriate Medicare coverage and payment for high-quality clinical laboratory tests. C21 appreciates the work of Novitas over the past decade in reviewing novel advanced diagnostic tests and establishing LCD policies, including its current LCD for oncology tests, "Biomarkers for Oncology" (L35396). C21 strongly supports the current LCD, and appreciates Novitas's willingness to identify individual tests as covered services based on its assessment of the analytical validity, clinical validity, and clinical utility evidence supporting each test. As we noted in our Open Meeting presentation, we are concerned that the proposed "Genetic Testing for Oncology" LCD would, if finalized, significantly limit beneficiary access to advanced diagnostic tests, including many tests performed by C21 members with longstanding Medicare coverage following a previous test-specific evidence review by Novitas.

Historically, it has been both CMS' and Novitas' position that unless an LCD explicitly identifies a test as a non-covered service following an individualized review of the evidence for that test, such test would be eligible for Medicare coverage on a case-by-case basis. C21 strongly supports this position. Moreover, in recent years this requirement has been codified in federal law, as the 21st Century Cures Act prohibits Medicare contractors from implementing non-coverage policies unless the contractor makes an evidence-based determination that a test does not meet the statutory/regulatory criteria for Medicare coverage.[2]

2. CONCERNS WITH PROPOSED LCD FRAMEWORK

a. Novitas should not issue a final LCD that delegates coverage decisionmaking authority to external databases – particularly insofar as the the LCD does not contain a viable, timely alternative pathway to coverage.

Under the proposed LCD, a genetic test must have adequate support in one of three databases to be covered: (i) National Comprehensive Cancer Network's (NCCN) database, (ii) National Institutes of Health (NIH)-sponsored clinical genome resource, ClinGen, or (iii) Memorial Sloan Kettering's tumor mutation database, OncoKB™. All tests not supported in one or more of these compendia would be presumptively non-covered, unless/until they successfully complete the LCD reconsideration process. This proposed coverage framework raises several concerns, including:

- *While third-party guidelines/recommendations can provide useful information when deciding whether to cover a test, relying solely on such determinations is not a*

[2] Social Security Act § 1862(l)(5)(D).

permissible substitute for evidence-based, test-specific review. Under the 21st Century Cures Act, MACs must include a "a summary of evidence that was considered **by the contractor** during the development of such determination and a list of the sources of such evidence" (emphasis added) as well as "[a]n explanation of the rationale that supports such determination."[3] Furthermore, while the Medicare Program Integrity Manual allows MACs to "supplement their research… with clinical guidelines, consensus documents, or consultation by experts," the Manual does not allow the MACs use these sources as a substitute for its own review.[4] Therefore, the decision to cover or not cover a particular test must be based on evidence reviewed **by Novitas**, and Novitas must memorialize its rationale by publishing an explanation for the decision. Relying on a third-party database without itself engaging in a test-specific evaluation or offering a test-specific rationale – as proposed – would be contrary to the Act, and amount to a preemptive non-coverage determination without the requisite test-specific, evidence-based review. Such reliance is particularly problematic insofar as there is no assurance that any of the compendia will have reviewed any individual test, particularly for novel assays.

- *Novitas does not have authority to delegate coverage decisions to third parties.* Congress delegated to the HHS Secretary the authority to "enter into contracts with any eligible entity to serve as a [MAC]" and establish LCDs.[5] Congress did not, however, grant the Secretary or the MACs the authority to delegate powers to other private parties. The U.S. Court of Appeals for the District of Columbia Circuit has stated that that "subdelegations to outside parties are assumed to be improper absent an affirmative showing of congressional authorization."[6]

  The court's concern is particularly relevant here. When private entities (like NCCN or MSK) update their databases, or NIH updates ClinGen, they are not required to comply with any of the procedural controls that normally apply to the development of LCDs. Specifically, they are:

  - Not required to issue a proposed decision that explains their rationale;
  - Not required to accept public comments on those proposals;
  - Not required to hold an open meeting to collect stakeholder feedback; and
  - Not required to consider and respond to public comments when finalizing their decisions.

  As a result, the decisions made by NCCN, MSK, and/or NIH are not subject to the same procedural controls and safeguards – and may be made with a different set of substantive considerations – than those that would have been required had the government's authorized delegate (Novitas) made the decision via the process required by law.

[3] *Id.*

[4] Medicare Program Integity Manual ch. 13, § 13.2.3.

[5] 42 U.S.C. §§ 1395kk-1(a)(1), (a)(4).

[6] *U.S. Telecom Ass'n v. F.C.C.*, 359 F.3d 554, 565 (D.C. Cir. 2004).

In support of its ability to delegate coverage decisions to third parties, Novitas points to Medicare's use of third-party compendia when deciding whether to cover certain chemotherapy drugs off-label.[7] However, this precedent is distinguishable from the diagnostic testing in three key respects.

- First, the Social Security Act explicitly requires Medicare to consider certain compendia when determining coverage for off-label uses for cancer chemotherapy drugs.[8] There is no analogous instruction that allows Novitas to use the compendia in the same way for clinical laboratory tests.
- Second, in the cancer drug context, the compendia are used to expand coverage beyond FDA-approved labeling for certain drugs – not to restrict coverage.
- And lastly, even if a particular off-label use is not supported in the compendia, Medicare explicitly retains the ability to review other published literature – i.e., Medicare is not solely bound based on the compendia's decision.[9]

- *Availability of the LCD reconsideration process is not an adequate alternative pathway to coverage.* Novitas states that interested stakeholders may request coverage for a test not supported in one of the three compendia via the LCD reconsideration process. However, this framework would not give test developers and other stakeholders an opportunity for public comment prior to implementation of non-coverage based on the compendia – even if the compendia themselves have not reviewed the evidence supporting a test. Therefore, reliance on the reconsideration process alone does not satisfy the requirement that MACs may not impose a policy restricting coverage for an item or service absent an evidentiary review. Rather, Novitas must review evidence, hold a public meeting, and consider public comment before making a non-coverage decision.

  Furthermore, Novitas makes no commitments regarding the timeframe on which it will substantively consider reconsideration requests, or how often it intends to update the LCD to reflect new evidence. MACs have 60 calendar days to determine whether a reconsideration request is valid.[10] Once determined to be valid, however, CMS does not require the MACs to substantively respond to a reconsideration request within any specific period of time. As such, reconsideration requests may remain in a MAC's queue for several months, if not longer, depending on MAC workloads and priorities. Furthermore, even once a MAC decides to substantively respond to a reconsideration request issuing a proposed LCD, that MAC has up to 365 calendar days to issue a final LCD.[11] As a result, tests not meeting compendia requirements may remain non-covered for multiple years, even if they otherwise have strong evidence supporting assay performance.

[7] Article – Response to Comments: Genetic Testing for Oncology (A59417).

[8] *See* Social Security Act § 1861(t)(2)(B) (applicable to Part B drugs); 1860D-2(e)(4) (applicable to Part D drugs); 1927(g)(1)(B) (applicable to drugs delivered to Medicaid beneficiaries).

[9] *See* Medicare Benefit Policy Manual ch. 15, § 50.4.5(C).

[10] *See* Medicare Program Integrity Manual ch. 13, §13.3.3.

[11] *Id.* §13.5.1.

- *NCCN is the only pathway to coverage for multianalyte algorithmic tests to obtain coverage.* Two of the three databases referenced by Novitas in the proposed LCD – ClinGen and OncoKB – do not review multianlayte algorithmic tests that may combine these variants with an empirically derived algorithm. These databases' restriction to single gene assays is plainly stated in their public-facing materials:

    - ClinGen: "We then use this data to answer a number of key curation questions: Is **this gene** associated with a disease, and by which mechanisms do variation cause this disease? Is **this variant** causative? Will this information affect medical management?"[12] (emphasis added)
    - OncoKB: "Alteration- and tumor type-specific therapeutic implications are classified using the OncoKB™ Levels of Evidence system, which assigns clinical actionability to **individual mutational events**."[13] (emphasis added)

  (At the Open Meeting, a speaker from MSK/OncoKB explained that database does account for certain concurrent gene-gene interactions in its reporting. The speaker did not, however, refute the point that OncoKB does not include recommendations multianlyte algorithmic tests.) As a result, multianalyte tests would only be eligible for coverage if supported in NCCN.

  Reliance on NCCN is not an appropriate substitute for evidence-based, test-specific review, as NCCN guidelines are largely consensus-based and may not reflect input from certain specialties or subsets of healthcare providers.[14] Indeed, NCCN itself acknowledges the limitations of this approach:

  > *The NCCN Guidelines® are a **statement of evidence and consensus of the authors regarding their views** of currently accepted approaches to treatment. **Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.** The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding*

[12] https://clinicalgenome.org/start/.

[13] https://www.oncokb.org/about.

[14] NCCN, Development and Update of Guidelines, https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines (last visited August 2023) ("Recommendations within the NCCN Guidelines are derived from critical evaluation of evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts and researchers in those situations where high-level evidence does not exist. Panels are charged with evaluating the efficacy of treatment, utility of tests or evaluations, and toxicity of the various interventions. Recommendations (or changes to existing recommendations) are agreed upon by Panel Members following review and discussion of the evidence during the Panel meetings. The Panel Members deliberate on the interpretation of the clinical evidence, and vote on how the evidence should be incorporated into the existing Guidelines. The Panel Chair and Panel Members then develop the wording to denote the specific recommendations within the Algorithms.")

> *their content, use or application and disclaims any responsibility for their application or use in any way.*[15]

Furthermore, updates to NCCN can be irregular, varying by disease state,[16] and standards for inclusion may vary significantly between different types of cancer (e.g., breast, bladder, prostate, cutaneous melanoma, and uveal melanoma). And lastly, NCCN guidelines may be challenging for providers (and Novitas itself) to faithfully translate into coverage policy, since certain guidelines are routinely updated, and the documents do not lend themselves to easy implementation of coverage policy (e.g., 84 guidelines consisting of 218 algorithms, as described by NCCN at the 2022 Open Meeting).

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Given the issues outlined above, we respectfully recommend that that Novitas withdraw the draft LCD at the end of the comment period, and convene one or more CAC meetings before engaging in future LCD development in this area. In the event that Novitas elects to finalize the draft LCD, however, we offer the following additional comments for your consideration:

- *The proposed LCD would identify tests supported by a majority of NCCN panel members as non-covered.* Novitas proposes to non-cover tests with a Category "2B" rating in NCCN. NCCN assigns a "2B" rating to tests for which there is NCCN "consensus" – i.e., 50-85% agreement – that the "intervention is appropriate" based on lower-level evidence.[17] It is unclear why Novitas believes tests supported by a majority (or potentially, a substantial majority) of NCCN panel members should be automatically non-covered. We encourage Novitas to remove the presumption against coverage for "2B" rated tests, and at minimum, review claims for such tests on a case-by-case basis consistent with longstanding Novitas practice.

- *The proposed LCD defines "screening" tests in a manner inconsistent with longstanding CMS policy.* The proposed LCD requires patients to have an "established a diagnosis of cancer or found significant evidence to create suspicion for cancer in their patient via a clinical evaluation and abnormal results (cancer or suspicious for cancer) from histologic and/or cytologic examination." In the "Response to Comments" article associated with the now-withdrawn version of L39365, Novitas takes the position that oncology tests performed prior to the availability of such evidence are "screening" tests:

> *Oncologic genetic testing is considered screening if it is performed before the ordering provider either establishes a diagnosis of cancer or a*

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[15] *See, e.g.,* NCCN Guidelines Version 3.2023: Bladder Cancer, https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf, at 3 (emphasis added).

[16] For example, the NCCN guidelines for rectal cancer have been updated 4 times since the start of 2023, while the guidelines for primary cutaneous melanoma have been updated just once (on January 5th, 2023).

[17] NCCN, Development and Update of Guidelines, https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines (last visited August 2023).

substantiated suspicion of cancer through histologic, cytologic, and/or flow cytometric testing.

Novitas's position is not consistent with CMS's longstanding definition of a "screening" test – i.e., a test for patients without "signs or symptoms" of the underlying condition.[18] Indeed, such signs or symptoms of cancer may exist without evidence from a "histologic and/or cytologic examination" – e.g., hematuria in patients suspected of bladder cancer. Therefore, if Novitas elects to finalize the LCD, we urge Novitas to remove the requirement for histologic and/or cytologic results, and permit evidence-based coverage for assays when run on patients with "signs or symptoms" of cancer.

- *Novitas's rationale for limiting coverage to these three specific databases – to the exclusion of all others – is not clear.* C21 appreciates the detailed assessment that Novitas conducted of each of the three databases, and agrees that all three databases may provide useful information to Novitas when evaluating the totality of the evidence supporting an individual test. However, dozens of other professional societies and guideline developers also make evidence-based recommendations regarding molecular diagnostic tests that reflect and/or inform the applicable standard of care, yet do not appear to have been evaluated for inclusion in the LCD. It is unclear why Novitas believes a favorable recommendation in an alternative evidence-based database or professional society guideline would not be sufficient to support a favorable coverage determination.

b. Evidentiary review of 13 specifically listed tests

In addition to our comments about the proposed LCD framework more generally, we offer the following comments in response to the test-specific evidentiary review for the 13 tests:

- *Novitas should restrict longstanding coverage only where supported by new evidence.* Several tests proposed for non-coverage in the draft LCD have been covered by Novitas for many years, including several for which Novitas initially decided to initiate coverage following a detailed review of the available evidence:

Test	Medicare Coverage Effective Date
DecisionDx-Melanoma	December 2018 (Palmetto)
DecisionDx-SCC	April 2022
Cxbladder Detect	July 2020

[18] *See, e.g.,* Screening for Colorectal Cancer – Stool DNA Testing (CAG-00440N), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=277 (last visited August 2023) ("This decision memorandum does not address the use of stool DNA testing as a diagnostic test to evaluate signs or symptoms of colorectal disease. (…) When making national coverage determinations concerning the scope of the CRC screening benefit under Medicare Part B, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that a test is appropriate for general screening in individuals with no signs or symptoms of colorectal cancer.")

Test	Medicare Coverage Effective Date
Cxbladder Monitor	July 2020
Cxbladder Triage	January 2023
PancraGEN	November 2010
UroVysion	July 2014
Colvera	January 2021

C21 agrees that Medicare coverage decisions should be made on the basis of the best available evidence, and therefore, it may be necessary to restrict or remove coverage. That being said, patients and providers alike rely on longstanding coverage determinations, particularly insofar as as such coverage was based on a review of the evidence supporting those tests. Therefore, existing test-specific coverage should be restricted only (a) if new evidence becomes available that reasonably questions whether an assay remains reasonable and necessary, (b) Novitas clearly identifies this new or updated evidence in a draft LCD, and (c) subjects any new or updated conclusions to public scrutiny via the LCD notice and comment process. Insofar as Novitas believes it has such grounds, we request that Novitas reissue the draft LCD to clarify these considerations.

- *Novitas must apply a consistent standard of review to all tests within the scope of the proposed LCD – not a different (higher) standard for specifically reviewed tests.* For compendia-supported tests, Novitas assumes that tests are analytically valid if run in a CLIA-certified laboratory, because "CLIA includes an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval, and any other performance characteristics required for the test system in the laboratory that intends to use it."[19] However, this same presumption is not afforded to any of the thirteen tests that underwent Novitas's test-specific evidentiary review, even though each of these tests is also performed in a CLIA-certified laboratory. Insofar as Novitas believes performance in a CLIA laboratory is sufficient to establish analytical validity for compendia-supported tests, it should make similar assumptions when it conducts a test-specific evidentiary review.

- *Novitas must consider and substantively respond to stakeholder comments on its test-specific evidentiary review of the 13 tests.* At the Open Meeting, Novitas stated that it is particularly interested in reviewing "new evidence" not already listed in the bibliography of the LCD. C21 agrees that evidence not previously considered would be highly probative, but also believes Novitas must review and respond to all comments submitted on the LCD, including comments regarding:
    - The overarching framework for review of evidence (e.g., overall approach, level of evidence required);

[19] Article – Response to Comments: Genetic Testing for Oncology (A59417).

- Novitas's interpretation of the literature cited in the proposed LCD (e.g., if a cited article does not reflect the intended use population of the test, or has some other limitation that explains reported performance characteristics);
- Published literature not included in the LCD;
- Other clinical guidelines and consensus statements not referenced in the proposed LCD; and
- Clinician experience with such tests (even if unpublished).

Notwithstanding Novitas's prior review of certain documentation, nothing in the Program Integrity Manual allows Novitas to ignore or not respond to public comments supported by evidence, even if such evidence relates to data the MAC may have already considered.

- *Novitas must consider and respond to stakeholder feedback, even if unpublished.* While C21 agrees that published evidence is an important component of any evidentiary review for an LCD, nothing in the Program Integrity Manual explicitly prohibits MACs from considering unpublished feedback. Indeed, the Manual actually suggests that such review and response is required, as it requires MACs to respond to "all timely received public comments" in the comment/response article.[20]

c. Concerns with coding article

In the proposed coding article (DA59125), Novitas does not identify any "unspecified" laterality codes or codes for cancer of unknown origin as covered when reported for genetic testing services. Insofar as Novitas decides to finalize the LCD, we urge Novitas to add both sets of codes for the reasons set forth below.

When treating physicians are considering genetic testing for oncology patients, they are looking for specific genetic variants or signatures in the tumors in order to guide treatment. The specific location where the tumor originated is generally no longer relevant by the time patients are referred for genetic testing to guide treatment. For example, when a patient presents with advanced non-small cell lung cancer, the location of the original tumor (e.g., right upper lobe versus left lower lobe) is irrelevant to selecting an appropriate chemotherapeutic or immunotherapeutic regimen to be guided by genetic testing.

In addition, by the time a patient presents to an oncologist with advanced cancer, it may not always be clear at that point where the tumor originated. Therefore, when the treating physician refers patients for genetic testing at that point in the course of their disease, the treating physician may not specify the originating site of the tumor nor provide an ICD-10-CM code as the referring diagnosis that is specific to the laterality or location of the originating tumor. Novitas's proposal to exclude ICD-10-CM codes from the list of covered codes that describe unspecified sites (e.g., ICD-10-CM C34.00, C34.10, C34.30, C34.80, and C34.90 for malignant neoplasm of lung)[21] would negatively impact access to medically necessary genetic testing in such cases

[20] Medicare Program Integrity Manual ch. 13, §13.5.5.

[21] **C34.00** *"Malignant neoplasm of unspecified main bronchus"*
C34.10 *"Malignant neoplasm of upper lobe, unspecified bronchus or lung"*
C34.30 *"Malignant neoplasm of lower lobe, unspecified bronchus or lung"*

where the treating physician is unable to or otherwise does not provide more specific information to determine the laterality of the original tumor. And, as noted above, knowing and reporting the laterality of the original tumor is generally irrelevant to the purpose and use of genetic testing for patients with cancer. The testing is medically necessary consistent whether or not the originating site of the tumor was on the right or left or in an upper lobe or lower lobe.

Furthermore, some patients present with advanced cancer where the origin of the tumor is unknown (commonly referred to as Cancer of Unknown Primary). Under these circumstances, genetic testing can still help help guide treatment decision making. Exclusion of codes C80.0 *"Disseminated malignant neoplasm, unspecified"* and C80.1 *"Malignant (primary) neoplasm, unspecified"* would block access to genetic testing in this patient population for whom genetic testing may be critically important to guide therapy.

Consistent with our request, CMS covers both unspecified laterality codes and Cancer of Unknown Primary codes, where appropriate, for next generation sequencing tests covered under NCD 90.2.[22]

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C21 is grateful for the opportunity to comment on the proposed LCD, and would be pleased to meet with Novitas if it has any questions. Please contact me at hmurphy@c21cm.org or (916) 835-5117 should you have any questions or if we can provide you with further information.

Sincerely,

Hannah Murphy

C34.80 *"Malignant neoplasm of overlapping sites of unspecified bronchus or lung"*
C34.90 *"Malignant neoplasm of unspecified part of unspecified bronchus or lung"*

[22] *See* Transmittal 12184 (Change Request 13278) (Aug. 3, 2023), r12184otn.pdf (cms.gov), at pgs. 12-69.