Article - Response to Comments: MolDX: Molecular Testing for Solid Organ Allograft Rejection (A58778)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01911 - MAC A	J - E	American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands

Article Information

General Information

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Response to Comments: MolDX: Molecular Testing for Solid Organ Allograft Rejection

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Response to Comments

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The comment period for the MolDX: Molecular Testing for Solid Organ Allograft Rejection DL38629 Local Coverage Determination (LCD) began on 5/28/20 and ended on 7/12/20. The notice period for L38629 begins on 5/20/21 and will become effective on 7/04/21.

The title of the LCD was revised from MolDX: Liquid Biopsies for Solid Organ Transplantation to MolDX: Molecular Testing for Solid Organ Allograft Rejection.

The comments below were received from the provider community.

Response to Comments

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1	Article states: The following coding and billing guidance is to be used with its associated local coverage determination. Ksort and Prospera are clinical laboratory tests that have met the criteria for coverage established for use in patients with renal allografts and there is an indication for testing for rejection.	Thank you for your insightful comments and support for the policy. Regarding some of the specific topics raised: 1. While in conversation we may consider this policy a “foundational” one

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	1. SUPPORT I support the use of foundational policies (also known as Umbrella policies) for multiple tests in a test category. Foundational policies should be used when a family of tests with similar performance and indication can be defined. I suggest referring to the policy as a "Foundational Policy for multiple tests in a similar category at the opening of the LCD. Coverage of specific tests will be determined by an associated and linked Article." This makes it clear to the reader what they are getting into. I would consider calling these "umbrella" policies as the metaphor of an umbrella may be more clear than the metaphor of something being "foundational." If someone did not know your intention, and you said, "I"m going to write a foundational LCD this week" it would not be obvious what the intention was. **2. DON'T LEAVE CERTAIN TESTS OUT SELECTIVELY** Policies should encompass all tests in a category. In the case of solid organ transplants, Palmetto has an LCD for the CareDx "Allosure" kidney donor DNA test, and an LCD for the Natera "Prospera" kidney donor DNA test. It is concerning, and unclear, why only the Prospera test is imported into the article for the new Foundational LCD. The foundational (umbrella) LCDs for solid organ transplant should include BOTH the Natera Prospera test and the CareDx Allosure test, rather than leaving one behind under its own LCD. The tests are very similar. **3. ARTICLE BASED COVERAGE: UNIFORM ACROSS MACs and TRANSPARENT** The shift of specific coverage decisions to Articles (or indeed, only to the Master Edit File) is problematic, as it reduces transparency. For example, lab "C" may submit a Tech Assessment for coverage as a donor DNA solid organ test, but its coverage never appears. There is no public rationale for non coverage of "Test C" and the public has no chance to comment. Therefore, labs could potentially be treated unfairly in the process of article generation, due to the lack of public rationale or comment.	because it covers a range of services, we have never used this term in the past within the text of the policy, and using such terms (or "umbrella" as a similar term) may add additional confusion. There is nothing unique about the structure of this policy compared to future polices in development, and such a distinction may not carry much significance. 2. Thank you for identifying that certain tests were omitted from the initial draft Billing and Coding Article. This was an error, in part as a result of having too many individual policies for individual and similar services, which this policy seeks to eliminate. All allograft molecular testing will fall under scope of this policy. 3. Thank you for this comment as it highlights a misperception of what we are doing with this policy and its related Articles. First, neither the Article, nor the MEF, determine coverage. Coverage and coverage criteria are set in the policy, which itself must go through the comment period. These criteria are based on the published evidence. The MEF is an internal file necessary for claims processing and plays no part in determining coverage. Lastly, the Billing and Coding Article provides instructions to providers how to bill and code for services within the scope of the policy and does not play a role in determining coverage. Contractors must understand the services being performed and evaluate if they meet the coverage criteria set in the policy and if restrictions or exclusions apply based on the intended use of the specific test; this is the role of the Technical Assessment. As providers may need to understand how to properly bill or code such services, and for transparency related to such services is wanted by all parties, we strive to add as much information relating these tests into Articles.

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	In addition, it is important that MOLDX MACs have uniform coverage articles. It would be concerning if one MAC, for example Noridian, accepts 3 tests approved by MolDx and never accepts (never lists) a fourth test. Again, the problem is one of fairness, public comment, and transparency to ensure fairness. **4. SPECIFICS OF THIS POLICY** We agree with the coverage for "liquid biopsies to assess a transplanted allograft rejection status." There are currently well-validated tests being commercialized in this space that use a urine, rather than a blood sample, and use urine-based DNA (and other biomarkers) rather than plasma DNA alone. Because the main mechanisms, intentions, and indications are so similar, this LCD should be interpreted (A) that liquid biopsy MAY include liquids other than blood plasma, and that (B) multiple biomarkers (such as DNA plus another biomarker) are eligible for coverage. See Yang, Sarwal et al., Science Translational Medicine, 2020	4. Thank you for this comment. Because of this comment (and others below) the term "liquid biopsy" has been removed from the policy, and the current language is not specific to a methodology or substrate. The coverage criteria defines under what conditions such tests would be covered (demonstrating equivalency with established methods).
2	On behalf of the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP), we thank you for the opportunity to review and comment on the proposed policy for MolDX: Liquid Biopsies for Solid Organ Transplantation. The AMP is an international medical and professional association representing approximately 2,500 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from academic medicine, hospital-based and private clinical laboratories, the government and the in vitro diagnostics industry. The CAP is the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs. The CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and	Thank you for your comments and helpful suggestions. Regarding your specific numbered comments: 1. Cell-free DNA has been amended to "donor-derived cell-free DNA" (but for brevity is still subsequently referred to as cfDNA). 2. While you are correct that TAs are an established part of the MolDX process, we also understand that providers read these policies to understand the coverage decisions but also to learn the process to attain both coverage and reimbursement. We prefer to err on the side of caution and over-inform.

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	laboratory medicine worldwide. We are submitting joint comments because currently both our organizations share the same position regard this draft LCD. Both AMP and CAP commend Noridian for recognizing the role of plasma-based molecular diagnostic methods that help monitor solid organ transplant and provide information to help optimize immunosuppressive therapy in post-transplant Medicare beneficiaries. The coverage limitations outlined in the proposed policy is reasonable based on the current evidence. While we agree with the proposed policy as outlined, we request that [you] consider making the following changes. 1.The term "liquid biopsy" is not a precise terminology that lends itself to application in a medical policy. While definitions vary on the precise meaning of this term, it can broadly be thought of as collection of a body fluid sample to test for relevant biomarkers to inform patient management. It is most commonly applied to the collection of peripheral blood for analysis of cell-free circulating tumor deoxyribonucleic acids (DNA). The term cell free DNA is also not specific enough as it may be variously derived: for allograft rejection tests the target of interest is "donor derived cell free DNA" or ddcfDNA; for fetal (birth) defect screening in maternal blood the target is "fetal cell free DNA" and for tumors, the target is usually described as "circulating tumor DNA." **Recommend:** Please amend the term "liquid biopsy" to read "**donor derived cell free DNA**" as a more precise term that is more suitable for a medical policy and avoid referring to these tests as liquid biopsies or circulating tumor cell tests. 2.The last bullet in the coverage criteria states that a test must successfully complete a technical assessment that will ensure that analytical and clinical validity criteria are met to establish the test as reasonable and necessary. The Molecular Diagnostic Services (MolDX) Technical Assessment (TA) has been a well-established requirement of the MolDX program since 2011. Since that time, laboratory developed tests or tests with undefined or	

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	unproven clinical utility have had to undergo a TA to ensure coverage. The TA process is detailed on Noridian's website, which applies to all molecular diagnostic tests covered under MolDX. Therefore, we do not think it is necessary, nor is an LCD the appropriate place, to mention this requirement. **Recommend:** Remove the requirement that a test must successfully complete a TA, as it is redundant and unnecessary. Thank you again for the opportunity to review and comment on this proposed policy. We are happy to be of assistance in providing additional clinical or other information to assist you with this draft LCD.	
3	This letter is in response to the draft LCD – MolDx: Liquid Biopsies for Solid Organ Transplant and specifically addresses the establishment of a broad LCD covering organ rejection technologies. Innovation and improvement in transplantation has resulted from the current MolDx LCD policy development and review process. If broad umbrella LCDs reduce administrative burdens and speed evaluation of appropriate evidence, and are clear, they should be adopted. They will continue the beneficial impact of the MolDx Program. Any finalized umbrella LCD should result in the withdrawal or retiring of all previous coverage policies. This will provide clarity and fairness for providers of technologies and tests. Furthermore, any new umbrella policy should go to great lengths to ensure that access to services, previously established by local coverage determinations, is maintained via the new policy's coverage criteria and intended use. Many methods and analytes as well as sample types may develop adequate evidence to impact organ transplant assessment and management. Expert physician judgement should be enhanced and be recognized as an important component of coverage under the LCD. Products which use similar methods and meet evidentiary standards should be covered and none should be "preferred" by CMS or its contractors.	Thank you for your comments. Draft policies are to be considered a work in progress, and it is only through thoughtful feedback and critique that they can be improved and finalized. The final version of this policy includes considerable changes from the first to address some of the issues you raise. First, the final policy no longer specifies a methodology or sample type, which may be construed as "preferred", and any molecular diagnostic test for the use of allograft rejection in solid organs falls within scope of this policy. The evidentiary review is more heavily focused on ddcfDNA and recipient GEP, but that is more of a consequence of the literature. Citations now add digital droplet DNA testing and GEP on FFPE.

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	We support the view that umbrella LCDs can simplify the coverage and reimbursement process by CMS and speed improvement in care for beneficiaries. The proposed umbrella for organ rejection management requires significant refinement and clarity to meet the high standards that are required.	
4	This letter is in response to the draft LCD: MolDx: Liquid Biopsies for Solid Organ Transplant and specifically addresses the proposed coverage criteria relative to existing coverage established by Active LCDs. In December 2019, MolDx finalized coverage for Prospera™ with the following intended use and coverage criteria: *"This Medicare contractor will provide limited coverage for the Prospera™ donor-derived cell-free DNA test (dd-cfDNA) (Natera, Inc., San Carlos, CA) to supplement the evaluation and management of kidney injury and active rejection (AR) in patients who have undergone renal transplantation. It can inform decision making along with standard clinical assessments.* **Criteria for Coverage** *The Prospera™ assay is covered only when the following conditions are met:* *The patient has a renal allograft* *Physician-assessed pretest need to further evaluate patient for the probability of active renal allograft rejection"* In making this determination MolDx noted that Prospera™ has been validated to rule in or out active rejection when assessing the need for or results of a diagnostic biopsy. Additionally, MolDx noted the evidence for Prospera™ identifies both antibody mediated rejection (ABMR) and T-cell mediated rejection (TCMR) as well as being validated to detect subclinical AR (MolDx: Prospera). In addition, all renal allograft recipients were covered by this LCD who met the Coverage Criteria. However, the proposed coverage criteria included in the	Thank you for your helpful suggestions. The final draft of this policy has been amended to allow for a broader range of considerations consistent with prior coverage determinations. It now additionally contains two use cases consistent with the above, not tying its need to a biopsy. We additionally used some of the introductory language provided.

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	draft LCD represents a significant retraction in the active coverage established for Prospera™. This uniquely and substantially limits access to this technology for Medicare beneficiaries. The proposed language below would limit physician and patient access to a previously established medically necessary service as determined by MolDx: *"The test is being used in lieu of a tissue biopsy in a patient for whom information from a tissue biopsy would be used to make a management decision. In general this test should not be used in lieu of a protocol biopsy in transplant centers that do not have a management algorithm for using such biopsies."* Specifically, the current coverage available to CMS members via the Active LCD for Prospera™ does not require the test be used "in lieu of a tissue biopsy" but does in fact recommend use for assessing "the need for or results of" a diagnostic biopsy. Furthermore, the proposed language now limits utilization to "rule out" testing alone and does not allow for "rule in" testing described in the Prospera™ LCD. Similarly, current coverage contains no limitations based on the requirement of transplant center protocol biopsy. This language would limit physicians to using their discretion only "in lieu of a tissue biopsy" and not allow them to supplement their evaluation of a biopsy result. Finally, the proposed language would limit the use of tests for assessment of subclinical rejection which was noted by MolDx as being validated with Prospera™. Surveillance with protocol biopsies may identify patients with subclinical rejection. While these criteria may be relevant to some transplant rejection assessment assays based on their clinical validation cohort, there is no such limitation for Prospera™. To remedy the discrepancy in current coverage with that proposed in the draft LCD, Natera recommends replacing the current draft LCD **Coverage Indications, Limitations, and/or Medical Necessity** with language that reflects the broad intended scope of the policy and does not include coverage criteria that is only specific to individual test.	

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	We support the revision below that captures currently covered tests and describes the conditions for future tests in all solid organ transplant settings. **Coverage Indications, Limitations, and/or Medical Necessity** This Medicare contractor will provide limited coverage for NGS based liquid biopsies for solid organ transplant to supplement the evaluation and management of organ injury and active rejection (AR) in patients who have undergone transplantation. It can inform decision making along with standard clinical assessments. It may be used by physicians considering the diagnosis of AR, helping to rule in or out this condition when assessing the need for or results of a diagnostic biopsy. It should be considered along with other clinical evaluations and results and may be particularly useful in patients with significant contraindications to invasive procedures. **Criteria for Coverage** Liquid biopsies for solid organ transplant rejection assessment are covered only when the following conditions are met: The patient has a solid organ allograft Physician-assessed pretest need to further evaluate patient for the probability of active allograft rejection Thank you for your consideration of this request for revision and dedication to ensuring CMS members continue to have access to services that are clinically validated and have been established as reasonable and necessary.	
5	**Background**. MolDx currently has an open comment period in for "Liquid Biopsies for Solid Organ Transplantation". While [some contractors] have covered these types of tests for two years, the proposed LCD will consolidate coverage in one LCD for all current and future testing options.	Thank you for your comments. This policy does not limit coverage to blood-based tests and has been amended to allow a host of newer technologies to fall within scope.

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	We support LCD; request added text. We support the policies for liquid biopsies as a medically necessary test to monitor organ rejection. There are already multiple tests in this clinical area, and there will likely be new entrants on a rolling basis. Therefore, the hope is this class LCD would be general enough to capture all these different methodologies and sample types. New tests will still be closely reviewed by MolDx, but the proliferation of cumbersome lists of LCDs on the same topic can be avoided. We recommend language be general in regards to the analyte/analytes testing, as well as the sample type on include as many test as possible. As in other LCDs, coverage would apply to similar (but not identical) tests for the same indication following the same coverage reasoning. ▫ Recommendation 1. The current draft umbrella LCD is for liquid biopsies using molecular methods, including both cell-free DNA and gene expression. This allows appropriate flexibility. Please ensure that the final LCD is not accidentally made more narrow. For example, both plasma and other tissues/fluid sources need to be eligible for coverage. Cell-free DNA, and other biomarkers, might be included in some future covered tests. Such new assays can be covered under this umbrella LCD after appropriate technology assessments. ▫ Recommendation 2. We suggest that when this LCD is complete, the corresponding CareDx LCDs be deleted and coverage transferred to an article in this policy. ▫ Recommendation 3. We suggest that NephroSant be added to the coverage article that implements the umbrella LCD. The technical assessment documents is being submitted separately via the Palmetto TA process. I am attaching a published clinical validation paper (Yang et al., 2020, Science Translational Medicine) to this email that will be part of that technical assessment.	
6	I am concerned that the proposed coverage criteria of draft LCD restricts existing access for patients and impacts accepted standard of care for use of dd-cfDNA for transplant rejection assessment. The language in the draft LCD states: *"The test is being used in lieu of a tissue biopsy in a*	Thank you for your comments- the requested changes have been previously addressed.

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	patient for whom information from a tissue biopsy would be used to make a management decision. In general this test should not be used in lieu of a protocol biopsy in transplant centers that do not have a management algorithm for using such biopsies." This appears to be a step backwards from existing coverage for CMS members. Through multiple Local Coverage Determinations, patients and physicians currently have the ability to utilize dd-cfDNA rejection assessment tests to "rule in" or "rule out" active rejection. Additionally, current coverage includes no requirement that tests be used "in lieu of" a diagnostic tissue biopsy. On the contrary, current coverage allows these tests to be used to assess "the need for or results of" a diagnostic biopsy, a very significant distinction. With this in mind, I request the coverage criteria of the draft LCD be modified to state: Donor-derived cell-free DNA is covered to supplement the evaluation and management of kidney injury and active rejection in patients who have undergone renal transplantation. dd-cfDNA is covered only when: The patient has a renal allograft Physician assessed pretest need to further evaluate patient for probability of active renal allograft rejection.	
7	On behalf of CareDx, I am writing to comment on the LCD MolDX: Liquid Biopsies for Solid Organ Transplantation. We wish to thank you for the opportunity to comment. We appreciate the long-standing relationship with MolDX. We strive to represent the best in the field of transplantation and have built our business on quality products with significant clinical evidence. AlloMap gene expression measurement platform for heart transplantation is FDA cleared and has been covered by Medicare since 2006, before the advent of MolDx. AlloSure, a non-invasive assessment of rejection in kidney transplantation through donor-derived cell-free DNA has been covered since late 2017 through the MolDx Tech	Thank you for these very helpful suggestions, many that mirror other comments. Although we will keep all transplant-related molecular testing under this one policy, we hope that the significant effort made in updating this final policy is more in line with practice and provider/expert recommendation.

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	Assessment program. We hope that our experience provides valuable input to the process for a foundational policy that addresses liquid biopsy for solid organ transplantation. We strongly support the MolDX program's leadership in the field of molecular diagnostics, and the general concept of developing foundational policies such as this LCD. However, we would like to suggest a few important matters for consideration, most of which we see largely as clarifications. Patients who have had an organ transplant require lifelong immunosuppression therapy regimens. Insufficient immunosuppression leads to graft rejection yet conversely, these immunosuppressive drugs have known side-effects, both related and unrelated to immunosuppression. In particular, patients on long-term immunosuppression suffer increased rates of infection as well as increased rates of some cancers. This requires intermittent patient assessment obtaining numerous clinical data points regarding organ physiologic function, immune status, overall patient health, and the injury status of the grafted organ itself. Due to both the risk of organ rejection as well as immunosuppression, patients who have undergone a transplant are by nature medically complex and considered high risk under current COVID-19 protocols within hospitals and the healthcare system. Coverage of liquid biopsy test services for organs beyond the existing AlloSure coverage in kidney transplantation is urgent due to the impact of the COVID-19 pandemic on the care transplant recipients. Clinicians continue to avoid in-office visits and unnecessary biopsies by leveraging telemedicine services and remote blood draw for surveillance testing as an effective means of reducing non urgent interactions with the healthcare system. Creating a foundational policy will enable expedited review and coverage within defined parameters under the MolDx Tech Assessment Program. Below we propose changes to improve and streamline this proposed process. **<u>Proposed Policy Change:</u>** 1. Based on the composition of the existing draft, the SOT Liquid Biopsy LCD is intended to include cell-free DNA test	

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	as well as gene expression tests. a. As is currently the case in existing Final LCDs, we recommend these policies remain separated into two distinct coverage decisions as these tests represent different methods of testing and different use cases which are both currently included in Draft LCD. A. The two approaches are measuring **different aspects of organ rejection** and have even been shown to provide more strength when used in combination. • **dd-cfDNA**: Donor-derived cell-free DNA is a product of cell turnover and therefore a marker for graft injury. This marker of graft injury has been correlated with rejection in numerous studies and ongoing evaluation continues to identify additional clinical utility within concept of graft damage. • **Gene Expression Signatures:** Quantification of gene expression in blood cells is a measure of the recipient immune response. Although several tests have been described (AlloMap, TruGraf, kSORT), with some differing technical aspects, they each comprise complex gene signatures from immune cells. B. The **technical measurement methods** of cfDNA are very different from those required for RNA. • **dd-cfDNA** is an analyte at very low concentrations within the already low cfDNA in the plasma. Numerous techniques have been attempted over the years to quantify dd cfDNA levels. Today, NGS is the technique of choice for accurate and precise measurement of dd-cfDNA. Quantification of dd-cfDNA can be analytically validated given access to reference materials. Clinical validity is then assessed in the appropriate clinical samples using an analytically validated method. • **Gene expression** signatures require that the levels of numerous RNA species be quantified, usually by either qPCR, dPCR, microarrays, or RNA-seq, and then a complex algorithm applied to generate a derived score. Although analytical validity of the individual RNA level measurements can be defined, the derivation of the scoring algorithm is dependent on both the analytical measurement capability unique to the given testing method and the clinical data associated with the defined pathological situation. **Once derived, the algorithm and score must be validated in samples independent from those used in gene selection or signature derivation**. This analytical validation, training, and subsequent clinical validation are quite distinct from the process required for dd-cfDNA and it will be challenging to	

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	write well-considered technical assessment requirements that apply to both types of testing. C. The two approaches are believed to have **differing abilities to discriminate types of rejection**. Equal injury to the graft may be equally represented in dd-cfDNA, however the immune mechanisms of rejection differ significantly between T cell-mediated and antibody-mediate rejection. The treatment for T cell-mediated rejection differs from that for antibody-mediated rejection, with the former more established (i.e. bolus steroids or increased maintenance immunosuppression) and for the latter antibody-depletion and pharmaceuticals currently in clinical studies (i.e. IL-6 receptor blockers). The possibility that dd-cfDNA informs on both types of rejection, but complex gene expression signatures could be specifically designed to accommodate both of the major immune influences, may create differences in the technical assessment process of these assays. D. There are significant differences in the **complexity of interpretation**. Despite the challenging environment for accurate and precise quantification of dd cfDNA, the mechanism and interpretation as a graft injury marker is straightforward. However, gene expression signatures are interpreted based on the definition applied in the training set (and subsequently clinically validated). This leads to a significant requirement for validation and characterization of each gene expression signature based on the derivation and validation sets. This is especially important with reference to the inclusion and exclusion criteria for the populations used in the validation and any subsequent characterization. Based on these important differences between dd-cfDNA and gene expression tests, we recommend that it will be most effective for clinical care, technical assessment, and administration of these policies if they are separated. We propose two policies, one for "Liquid Biopsy", which would be expected to address dd cfDNA tests and future applications of straightforward DNA analytes in blood that are analytically validated independent of the clinical samples. The second policy would be for "Gene Expression Signatures" and would cover RNA measurement tests that incorporate a unique signature, algorithms, and scoring mechanism producing a patient specific risk score.	

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	<u>Proposed Policy Clarifications:</u> 2. Within the context of the two separate policies, we recommend that the following statement be clarified: *"This Medicare contractor will provide limited coverage for liquid biopsies to assess a transplanted allograft for rejection status when the following criteria are met:"* Specifically, we recommend clarification of the term: "liquid biopsies." We believe based on the review of the evidence that Palmetto GBA specifically meant tests of donor derived cell free DNA and/or RNA performed on a specimen obtained from blood or serum. As such, we would request that the phrase above read as follows in the recommended two separate LCD: **cfDNA:** *"This Medicare contractor will provide limited coverage for blood-based molecular assays of DNA, from here on called "liquid biopsies," to assess a transplanted allograft for rejection stats when the following criteria are met"* **RNA:** *"This Medicare contractor will provide limited coverage for blood-based molecular assays of RNA, from here on called "gene expression signatures," to assess a transplanted allograft for rejection stats when the following criteria are met"* 3. The 4th bullet point under the coverage criteria currently reads as follows: *The test is being used in lieu of a tissue biopsy in a patient for whom information from a tissue biopsy would be used to make a management decision. In general, this test should not be used in lieu of a protocol biopsy in transplant centers that do not have a management algorithm for using such biopsies.* The idea "in lieu of" is inaccurate and may be interpreted in a way that was not intended. While transplant centers do have management protocols for transplant patients, these protocols have varying degrees of specificity and they change over time, specifically now in the era of high-risk patients managed under new and sometimes temporary medical center policies. Moreover, transplant patients are not managed solely by transplant center	

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	protocols but by collaborating clinicians at these institutions, including numerous transplant physicians who may increase or decrease patient treatment and monitoring based on a host of clinical factors. Clinicians must make individualized patient-specific decisions when caring for each transplant patient. These are complex decisions requiring a mix of tests including laboratory tests performed on blood (or serum) and urine as well as imaging tests, which sometimes include or recommend a biopsy. The particular tests ordered for any given individual at a particular point in time will be driven by the patient's baseline risks for complications, risk of rejection and the patient's current clinical status. There are sometimes also practical concerns of whether or not a patient is willing or able to receive a particular diagnostic test. In summary there may be varying degrees to any institutional protocol in the management of a given patient as these vary from physician to physician and across transplant centers nationwide. While we recognize that it is not the intent of this criterion to limit patient access, and we hope that the risk to patients due to the current COVID pandemic is temporary, however we feel it important to highlight the concerns to the current draft which may create barriers to patient/provider access in a critical period when telemedicine and remote testing has been the cornerstone of uninterrupted patient care. This is neither consistent with the current state of practice nor with the laws themselves. It appears that the overall goal of this coverage criterion is to ensure that the information obtained from the liquid biopsy or gene expression signature is used by a transplant clinician in the process of deciding how to manage a patient. As such, we would like to propose language making that clinician judgement regarding the need for information in a clinical decision determines whether the test is reasonable and necessary, and not institutional policy or protocol. We recommend the following revisions to this bullet point: For Liquid Biopsy: *A clinician treating the patient for transplantation is using*	

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	the test to gain information and guide treatment decisions regarding the status of the transplanted organ or as an indicator of allograft rejection. This information must be used in clinical management regarding the donor organ. A liquid biopsy may be used in conjunction with clinical information and information obtained from other diagnostic tests. For Gene Expression Signatures: *A clinician treating the patient for transplantation is using the test to gain information and guide treatment decisions regarding the immune response of the patient to the allograft or as an indicator of graft rejection. A gene expression signature may be used in conjunction with clinical information and information obtained from other diagnostic tests.* 4. The analytical and clinical validity under coverage criteria are combined, and currently read: • *The test demonstrates analytical validity, including an analytical and clinical validation, and has demonstrated concordance with either tissue or another already-accepted standard for the intended use with the study published in a peer-reviewed paper. The tissue must be assessed using the Banff classification for renal allografts or equivalent accepted criteria for other organs.* • *The test has demonstrated clinical validity in that the test provides information about at least one of the two following clinical status determinations:* *o Rejection status* *o T-cell mediated vs B-cell mediated rejection* • *The test is being used in a patient who is part of the population in which the test was analytically validated and has demonstrated clinical validity* Analytical and clinical validity can sometimes be distinctly evaluated and may have separately considered criteria. We therefore recommend these bullets be separated and clarified for the two types of validation. For Liquid Biopsy: • *The test demonstrates analytical validity using orthogonally quantified reference material that encompasses the range of the application* • *The test demonstrates clinical validity through*	

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	concordance with an accepted standard for the intended use, and with the study published in a peer-reviewed journal. If this standard is histology, obtained through tissue biopsy, the tissue must be assessed using the Banff classification for renal allografts or equivalent accepted criteria for other organs. *• The test has demonstrated clinical validity in that the test provides information about overall rejection status.* *• The test is being used in a patient who is part of the population in which the test has demonstrated clinical validity. Clinical validation studies should be representative of demographics, disease, treatments, and morbidity in the wider population to ensure true clinical validity.* For Gene Expression Signatures: *• The test demonstrates analytical validity for quantified RNA measurement within the applicable range of the intended use* *• The test demonstrates clinical validity through concordance with an accepted standard for the intended use, and with the study published in a peer-reviewed journal. If this standard is histology, obtained through tissue biopsy, the tissue must be assessed using the Banff classification for renal allografts or equivalent accepted criteria for other organs.* *• The test has demonstrated clinical validity in that the test provides information about overall rejection status.* *• The test is being used in a patient who is part of the population for which the test was developed (including gene selection, signature training, and signature testing), and who is part of the population in which the test demonstrated clinical validity. Clinical validation studies should be representative of demographics, disease, treatments, and morbidity in the wider population to ensure true clinical validity.* **Comments on the evidentiary basis for liquid biopsies for solid organs:** Solid organ graft survival has improved since the advent of transplantation, which has been attributed to improvements in allograft care. Allograft rejection can be T-cell-mediated (TCMR) or antibody mediated (ABMR). Immunosuppressive therapy targeting both TCMR and ABMR has clearly been part of this improvement, though graft rejection remains a considerable challenge in the management of transplanted patients. Challenges surrounding immunosuppression are largely due to the	

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	fact that inadequate immunosuppression may lead to rejection, but immunosuppressive treatment itself is associated with other serious health problems including infection and renal insufficiency. The AlloSure assay has been well validated as a non-invasive test that provides information about the rejection status of a grafted heart, kidney or lung. Gene expression signatures such as AlloMap Heart are panels of genes which have been proven to detect changes in gene expression associated with acute rejection and provide an actionable risk score giving physicians information on the risk of acute cellular rejection in their patients following transplant. Timely detection of allograft rejection is associated with improved graft survival, and even subclinical rejection has an important impact on graft survival. Liquid biopsies using both cell free DNA and gene expression profiling have shown that they can provide meaningful information in allograft recipients to assist clinicians in the management of immunosuppression of a transplanted organ.	
8	Please accept this comment letter addressing proposed CMS coverage of Liquid Biopsies for Solid Organ Transplant. The concept of broad "umbrella" LCDs that speed access for patients and adoption of advancing technologies is a welcome prospect. Concerns over reducing existing access must be addressed and every measure should be taken to ensure existing coverage criteria are maintained under these new "umbrella" policies in order to maintain existing standards of care. With the introduction of broad coverage policies that are intended to include multiple use scenarios and technology platforms it is equally important to create policies that take into account current "proprietary" LCDs. Not doing so would give the impression of "preferred" status for policies written for specific products/services relative to competitive products covered only under "umbrella" policies.	Thank you for your comments. We hope the changes made in the final version of this policy is more in line with your expectations.

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	Many methods and analytes as well as sample types may develop adequate evidence to impact organ transplant assessment and management. Expert physician judgement should be enhanced and be recognized as an important component of coverage under the LCD. Products which use similar methods and meet evidentiary standards should be covered and none should be "preferred" by CMS or its contractors. I support the view that umbrella LCDs can simplify the coverage and reimbursement process by CMS and speed improvement in care for beneficiaries. The proposed umbrella for organ rejection management requires significant refinement and clarity to meet the high standards that are required.	
9	Immucor, Inc. a global leader in transfusion and transplantation diagnostics, applauds Palmetto/MolDX's publication of Liquid Biopsies for Solid Organ Transplantation and appreciates the opportunity to submit the following comments in support of this LCD. Kidney (renal) transplantation is the current gold standard therapy for American patients diagnosed with end-stage renal disease (ESRD), including nearly 500,000 patients for whom Medicare is the primary or secondary healthcare payer of record. Although kidney transplantation is both clinically and economically beneficial for many patients, a portion of transplant recipients may experience acute rejection (AR), marked by patient's immune systems rejecting the donor organ at varying time points post-transplantation. AR is an adverse outcome and is demonstrably correlated with interstitial fibrosis and tubular atrophy (IF/TA) incidence and broader unfavorable effects on patient quality of life and total cost of care. Further, the less-well-defined classification of chronic rejection contributes to the drop in long-term graft survival rates for patients to nearly 50% by 10 years post-transplant, underscoring the need for effective surveillance tools that can be used on this patient population long-term following a transplant. Invasive renal allograft needle biopsy is the most widely used methodology for diagnosing AR. Unfortunately, the	Thank you for your comments.

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	inherent nature of needle biopsy exposes patients to risks including infection and undesired graft damage potentially resulting in bleeding or arteriovenous fistula. Additionally, a substantial body of research indicates needle biopsy is further limited by its high sampling error rate, which compromises clinical utility and often requires repeat biopsies that may also produce nonactionable results or further adverse event risks. Despite this landscape, for-cause and protocol biopsy remains as the diagnostic guide for clinical decision-making regarding the use of potentially harmful immunosuppression to address AR. The clinical biopsy decision process can essentially be broken down into three states: healthy patients with non-concerning laboratory values, who are not recommended for biopsy; sick patients with concerning lab values, who are always recommended for biopsy; and patients with statuses falling between those categories, whose biopsy recommendations are less likely to provide a treatable cause for their status. Directly addressing the critical unmet clinical need for additional, non- and minimally-invasive tools to help inform clinician decision-making, Immucor offers kSORT, a whole blood-based, gene expression assay through its CLIA-certified and CAP-accredited clinical reference laboratory, ImmucorDX (Grand Rapids, MI). kSORT's analytical and clinical validation and utility is supported peer-reviewed clinical studies, included those cited within MolDx's draft determination. Evaluation of transplant recipients' kSORT-provided dynamic immune risk profiles, combined with best practice clinical care, is expected to improve acute transplant rejection risk stratification and accelerate selection of appropriate clinical decision-making, leading to improved clinical and health economic outcomes among this patient cohort. Immucor appreciates the efforts of MolDx and its partners to also provide complimentary clarity regarding coding and reimbursement processes for liquid biopsy assays for solid organ transplant indications. We appreciate the recent publication of [the article], a draft guidance document, and look forward to similar complimentary guidance from [other contractors] supporting healthcare provider utilization of a final version of the proposed draft LCD. Finally, we remain committed to sustained development of	

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	molecular diagnostic solutions for renal transplantation management and other needed clinical applications, and look forward to MolDx's continued administrative collaboration. Immucor welcomes the clarity provided by the proposed LCD, establishing coverage for kSORT and other evidence-based liquid biopsies with demonstrated value.	
10	On behalf of Eurofins Scientific's U.S. Clinical Diagnostics division, I respectfully submit the following comments in response to the above-captioned proposed LCD. Our comments are specifically submitted on behalf of our two laboratories offering post-transplantation diagnostic testing: (i) Viracor Eurofins, Inc., a CAP-accredited, CUA-certified clinical laboratory located in Lee's Summit, Missouri, and (ii) Transplant Genomics Inc., a CAP-accredited, CUA-certified clinical laboratory located in Fremont, California. Both Viracor Eurofins and Transplant Genomics have tests that could fall under the proposed LCD, but we believe they should be treated differently. In the landscape of diagnostics for post-transplant rejection testing, we believe there are two principal types of tests that are available to physicians, with the key differentiation being the patient population or context of use, i.e. whether the patient presents with the suspicion of kidney rejection (e.g., elevated creatinine indicating acute rejection) versus stable kidney function (where subclinical rejection may be present).1·2 This distinction is important, because serial monitoring of patients and/or replacement of surveillance biopsies should be exclusively the domain of tests that are validated in patients with stable kidney function3•4, while tests that evaluate a suspicion of rejection (e.g., elevated creatinine) should be limited in their use to precisely that context of use and patient population5•6. We believe that the proposed LCD well addresses the category of suspected rejection based on clinical factors, with some recommended redline changes that are attached to this emailed letter. However, we do not believe the proposed LCD appropriately addresses testing for patients with stable kidney function, and attempts at combining the two different diagnostic test categories risks (i) overutilization of tests whose utility is for confirming suspected active rejection, and would not require serial testing, or (ii) inappropriate utilization of a diagnostic test used to confirm suspected acute rejection on a patient with stable kidney function, and vice versa. As such, we recommend revising the draft LCD to clarify	Thank you for your comments. This policy was not intended to rescind coverage for tests used for low-risk patients using such tests for surveillance, and the coverage criteria, and evidentiary review, has been altered to reflect this.

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	that it only applies to patients for whom rejection is suspected based on at least one clinical factor. **Eurofins Viracor's TRAC test:** The proposed LCD sets forth Medicare coverage criteria for "liquid biopsies to assess a transplanted allograft for rejection status." Viracor Eurofins performs the Transplant Rejection Allograft Check (TRAC™) donor-derived cell-free DNA (dd-cfDNA) test, which uses next generation sequencing (NGS) and genomewide recipient genotype data to determine the percentage of dd-cfDNA present in plasma from transplant recipients, including kidney, lung, liver and heart transplant7. Because a donated organ releases dd-cfDNA when attacked by antibody or cell-mediated rejection processes, the percentage of dd-cfDNA found in a patient's plasma may help physicians identify patients experiencing solid organ transplant rejection. Therefore, Viracor Eurofins believes that the proposed LCD would be applicable to TRAC™ (if finalized).8 Viracor intends to submit a Technology Assessment (TA) to MolDX that establishes the performance of TRAC™ under the proposed LCD. Viracor encourages MolDX to start reviewing this TA immediately upon receipt - i.e., even if received while this LCD remains in draft form - to expedite beneficiary access to the test upon finalization of the LCD and TRAC™'s successful completion of the TA process. **Transplant Genomics' TruGraf Test:** MolDX finalized an LCD for TruGraf Blood Gene Expression Test on November 25, 2019. TruGraf uses DNA microarray technology to measure differentially expressed genes in the blood of renal transplant recipients to identify patients who are likely to be adequately immunosuppressed.3•4 Lastly, research and development in which additional biomarkers are incorporated to enhance the performance (NPV /PPV) of TruGraf (preliminary and unpublished) would further amplify the difference between the two contexts of use (TruGraf in stable patients and cfDNA in patients with a suspicion of rejection). This advancement will create the first rule-in test for organ rejection, and is only meaningful in the stable patient cohort, because it will indicate with high confidence that an otherwise healthy kidney is, in fact, rejecting. This type of test would be new evidence to in which to inform the use of the other test, because it will have demonstrated a suspicion of rejection. For the reasons outlined above, we do not believe the draft LCD should address patients with stable function, and	

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	encourage MolDX to (a) retain [the LCD] as an active, stand-alone LCD, and (b) clarify that the draft LCD does not apply to tests performed on patients with stable function. In addition to the comments set forth above, we have recommended certain technical changes to the draft coverage language (i.e., deletion of the phrases "in lieu of a tissue biopsy in a patient for whom information from a tissue biopsy would be used" and "in transplant centers that do not have a management algorithm for using such biopsies" from the fourth bullet) in the attached redlined document. Our rationale for these changes is set forth in the document itself. Finally, please note that we have provided these comments and the attached redline under the assumptions that (a) the draft LCD only addresses coverage for patients suspected of organ rejection (and not those stable transplant function) and (b) that the existing TruGraf LCD will remain active and effective regardless of whether this draft LCD is finalized. However, if that is not the case, we encourage MolDx to avoid making any changes that would limit the existing coverage for TruGraf, which MolDX established after reviewing a TA establishing the performance of TruGraf.	
11	Thank you for the opportunity to submit comments regarding MolDx Proposed LCD Liquid Biopsies for Solid Organ Transplantation. I am formally submitting these comments for consideration in my role as a nephrologist – researcher with a focus on organ transplantation and organ diseases, including the mechanisms of organ transplant rejection and injury, and the development of treatments to improve outcomes in transplantation and primary organ diseases. Through my work I have developed the Alberta Transplant Applied Genomics Centre (ATAGC), the center for molecular studies of organ transplants and organ diseases at the University of Alberta. In addition to my role as the founding Editor-in-Chief of the American Journal of Transplantation from 2000 to 2010, I am the developer of the Molecular Microscope® Diagnostic System (MMDx), a system for reading organ transplant biopsies using microarrays that is now being licensed commercially.	Thank you for your comments. The policy has been amended based on the comments received to be broader in scope for allograft testing. As such, the test described above would fall within scope of this policy. However, the language regarding tissue type has been redacted to be compatible with other novel test types.

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	Liquid biopsy assays have an important role for use as screening tests to assess abnormalities in a transplanted organ. While liquid biopsies can be used successfully for screening, they lack the required specificity to distinguish various forms of disease and injury from each other. A liquid biopsy is not equivalent to a molecular assessment of the tissue for the assessment of the transplanted organ. As a result, I respectfully request that the Molecular Microscope® Diagnostic System (MMDx) be considered outside of this proposed LCD for the following reasons: 1. MMDx relies on a tissue biopsy sample to assess rejection and injury in a transplanted organ. The proposed LCD clearly distinguishes between liquid and tissue biopsies. Therefore, MMDx should not be included under this new LCD because it is not a liquid biopsy. The liquid biopsy is always a screening test and can never provide a definitive answer, only the probability of abnormality. These terms describe separate types of clinical samples retrieved for very different diagnostic workflows, tests, and diagnoses. Liquid biopsies describe fluid samples (i.e. blood) taken to look for biomarkers in the sample (e.g. cell-free DNA, circulating tumor cells, etc. (1)) and are used commonly in cancer diagnostics, and more recently in transplantation. These samples are suitable for a variety of assays that do not necessarily overlap with assays used for tissue biopsy analysis, and are accompanied by unique challenges (2-4). Tissue biopsies such as MMDx represent a distinct diagnostic testing method (5-10) and should not be regarded as replaceable by liquid biopsies, which are screening tests to guide the decision to perform a biopsy. 2. As stated in the proposed LCD document, the liquid biopsy test "is being used in place of a tissue biopsy in a patient for whom information from a tissue biopsy would be used to make a management decision. In general, this test should not be used instead of a protocol biopsy in transplant centers that do not have a management algorithm for using such biopsies." The liquid biopsy is inherently a screening test to determine whether a definitive tissue biopsy should be performed. Liquid biopsies can therefore inform decisions for definitive tissue assessment by MMDx, but the screening test cannot replace the definitive biopsy assessment in many cases, only guide whether a tissue biopsy is likely to	

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	be useful. While liquid biopsies can be used successfully for screening, they lack the required specificity to distinguish various forms of disease and injury from each other. This ability to separate types of disease and injury is a feature of the MMDx tissue biopsy assessment. 3. As stated in the document "The benefit to risk profile of the liquid biopsy is considered by the ordering clinician to be more favorable than the benefit to risk profile of the tissue biopsy…", That is a general feature of all screening tests. But the clinician requires an accurate and quantitative assessment of the disease states that require treatment. This ultimately requires a tissue biopsy and MMDx is the next generation of tissue biopsy assessments. Liquid biopsies guide the decision to biopsy the tissue. MMDx provides the definitive assessment of rejection and injury states in the tissue.	
12	I would strongly consider the change in coverage criteria to allow physicians use cell-free DNA to improve kidney transplant patient outcomes. I am concerned that the proposed coverage criteria of draft LCD restricts existing access for patients and impacts accepted standard of care for use of dd-cfDNA for transplant rejection assessment. The language in the draft LCD states: "The test is being used in lieu of a tissue biopsy in a patient for whom information from a tissue biopsy would be used to make a management decision. In general this test should not be used in lieu of a protocol biopsy in transplant centers that do not have a management algorithm for using such biopsies." This appears to be a step backwards from existing coverage for CMS members. Through multiple Local Coverage Determinations, patients and physicians currently have the ability to utilize dd-cfDNA rejection assessment tests to "rule in" or "rule out" active rejection. Additionally, current coverage includes no requirement that tests be used "in lieu of' a diagnostic tissue biopsy. On the contrary, current coverage allows these tests to be used to assess "the need for or results of" a diagnostic	Thank you for your comments. These have been addressed with comments above.

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	biopsy, a very significant distinction. With this in mind, I request the coverage criteria of the draft LCD be modified to state: Donor-derived cell-free DNA is covered to supplement the evaluation and management of kidney injury and active rejection in patients who have undergone renal transplantation. dd-cfDNA is covered only when: The patient has a renal allograft Physician assessed pretest need to further evaluate patient for probability of active renal allograft rejection. Thank you for consideration of this request for revision.	

Associated Documents

Related Local Coverage Documents

LCDs

L38629 - MolDX: Molecular Testing for Solid Organ Allograft Rejection

Related National Coverage Documents

N/A

Public Versions

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