Laboratory Testing for Transplant Rejection

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DESCRIPTION

Transplant rejection involves an immune response to a transplanted organ. The recipient's immune system recognizes the donated organ as "foreign," thereby initiating an immune response as if the transplant organ was a foreign antigen. This response may cause the organ transplant to fail. Gene expression profiling (GEP), donor derived serum cell-free DNA (dd-cfDNA), breath testing, and urine-based assays have been proposed as a possible way to monitor organ transplant rejection non-invasively.

Solid organ transplant requires much oversight and evaluation. Rejection, or failure of the transplant, is a potential outcome of any transplant case. At the molecular level, rejection is primarily caused by a component of the adaptive immune system, the major histocompatibility complex (MHC) proteins. These proteins must match between the donor and recipient, or the transplant can fail.

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The MHC proteins' primary function is acting as the platform on which T-cells identify antigens. Typically, these MHC proteins bind foreign antigens, which are then recognized as such by T-cells. From there, the T-cells can generate an immune response to handle the antigen. However, the MHC protein products must be identified as "self" by these T-cells as well. If an organ donor's MHC protein does not match the recipient's, the recipient's T-cells may identify the MHC of donated organ as "foreign" and subsequently implement an immune response. This eventually starts the cascade of events that causes the transplant to fail.

Numerous methods mitigate this immune response such as immunosuppressants, which cause desensitization of the immune response. Other methods involve evaluating the risk of organ transplant rejection using gene expression profiling (GEP), donor derived serum cell-free DNA (dd-cfDNA), breath testing and urine-based testing evaluation which include the following:

Breath Testing

- **Breath methylated alkane contour (BMCA) (e.g, Heartsbreath)**: Is a test that is purportedly indicated for use as an aid in the diagnosis of *grade 3 heart transplant rejection* in individuals who have received a heart transplant within the preceding year. It is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy (EMB). The use of the test is limited to individuals who have had endomyocardial biopsy within the previous month. By breathing into a plastic mouthpiece that is attached to a breath collecting device, the amount of methylated alkanes that is in the individual's breath is supposedly subtracted from that found in the room. A value is then generated and is compared to the results of a biopsy performed during the previous month to measure the probability of the implanted heart being rejected.

Donor Derived Cell-Free DNA (dd-cfDNA) Tests

- **Allosure Heart:** Purportedly determine allograft injury by measuring donor-derived cell-free DNA (dd-cfDNA). These tests reportedly are indicators of organ injury, with the goal of predicting active rejection of the heart.
- **Allosure Kidney**: Is a donor-derived cell-free DNA (dd-cfDNA) test for noninvasive kidney transplant surveillance, providing a direct measure of organ injury, with the goal of predicting active rejection of the kidney.
- **Allsure Lung**: Is a donor-derived cell-free DNA (dd-cfDNA) test for noninvasive lung transplant surveillance, providing a direct measure of organ injury, with the goal of predicting active rejection of the lung.
- **MyTAIHeart Test:** This test analyzes the release of donor-specific cell-free DNA in the blood of individuals with a heart transplant before and after receiving heart biopsies. The test is sensitive to injury to the donor organ.
- **Prospera (Natera)**: Is a donor-derived cell-free DNA (dd-cfDNA) transplant rejection test. Prospera increases a provider's ability to identify otherwise undetected rejection that might lead to kidney loss. Catching transplant rejection

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as soon as possible can help providers develop a treatment plan to be protect the donated kidney.

- **Viracor TRAC:** Is a donor-derived cell-free DNA (dd-cfDNA) assay that determines the percentage of circulating cell-free DNA (cfDNA) in transplant recipients derived from donor grafts for heart, kidney, and lung. cfDNA is extracted from plasma isolated from whole blood collected in Streck BCT tubes within seven days of collection and unbiased sequencing is performed. Next Generation Sequencing (NGS) and genome-wide recipient genotype data are then analyzed by a bioinformatics pipeline that calculates the percentage of dd-cfDNA present to determine injury to the donor organ.

Gene Expression Profiling

- **Allomap (CareDx):** Is a panel of 20 genes, 11 informative and 9 used for normalization and/or quality control, which produces gene expression data used in the calculation of an AlloMap test score – an integer ranging from 0 to 40. Compared with individuals in the same post-transplant period, the lower the score, the lower the probability of acute cellular rejection at the time of testing. The clinician uses the AlloMap score, along with other standard clinical assessments, to evaluate the individual's probability of rejection and the need for additional diagnostic evaluations. It is hoped the results of this test will decrease the number of necessary endomyocardial biopsies (EMBs). It has been recognized that the test is not effective at monitoring rejection within the first 6 months of transplantation,

Immune Response Gene Expression Panel

- **nCounter Human Organ Transplant Panel:** Is a gene expression panel profiling 770 genes across 37 annotated pathways to discover biomarkers for organ rejection and tissue damage for kidney, heart, liver and lung. Also, identifies BK Polymavirus, Cytomegalovirus (CMV) and Epstein Barr-Virus.

Molecular Gene Expression Assay

- **Kidney Solid Organ Response Test (kSORT):** Has been developed for kidney transplant rejection to purportedly detect individuals who are at high risk for acute rejection. Polymerase chain reaction (PCR) is utilized to measure the relative mRNA expression levels of 17 genes that have been known to be associated with acute rejection. Individuals are classified into high, low or indeterminate risk according to a correlation-based algorithm.

Molecular Microscopic Diagnostic System (MMDx) Heart; Molecular Microscopic Diagnostic System (MMDx) Kidney; Molecular Microscopic Diagnostic System MMDx Lung: Utilizes proprietary microarrays and algorithms based on a reference set of biopsies to provide scores of probabilities of rejection by reportedly measuring cell-mediated rejection. The tests are purportedly utilized for heart, kidney, and lung transplants.

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mRNA Gene Expression

- **Clarava:** Clarava (Verici Dx) is a pre-transplant, peripheral blood, prognosis test for the risk of early acute rejection for kidney transplants using RNA expression by select transcriptome sequencing.
- **TruGraf Blood Gene Expression Test**: TruGraf is a non-invasive test that measures differentially expressed genes (107 genes [mRNA) related to inflammatory pathways) in the blood of kidney transplant recipients to identify individuals who are likely to be adequately immunosuppressed and, in doing so, rule out graft damage. TruGraf measures the difference in gene expression to discriminate between allografts that are truly healthy (Transplant eXcellence, or TX), and those in transplant individuals that are "silently" sub-clinically rejecting (not-TX) with no other suspicion of rejection.
    - Transplant eXcellence (TX) means that the transplanted organ is expected to be adequately immunosuppressed
    - not-TX means that the transplant organ is likely to be inadequately immunosuppressed
    - Transplant clinicians benefit by stratifying individuals into those who may benefit from surveillance biopsy and those who likely will not, allowing them to eliminate a large percentage of surveillance biopsies that would likely have been negative if performed.
- **Tuteva:** Tuteva (Verici Dx) is a post-transplant, peripheral blood, prognosis upon acute cellular rejection for kidney transplant recipients, including sub-clinical rejection as correlates to histopathology findings by using RNA expression by select transcriptome sequencing.

Urine- Based Tests for Allograft Rejection

- **QiSant (also known as Qsant):** Several urine-based tests have been proposed utilizing various biomarkers to aid in the diagnosis of acute rejection in kidney transplant recipients. Purportedly, the tests measure urine mRNA, urine proteins and/or urine proteomics. Some tests measure several biomarkers (e.g.,, QiSant [also known as QSant]) to reportedly determine acute kidney transplant rejection. The biomarkers include, but may not be limited to, cfDNA, methylated cfDNA, clusterin, CXCL10, creatinine and total protein, which are integrated into an algorithm to supposedly determine kidney risk rejection scores.

Clinical Context and Test Purpose

The purpose of gene expression profiling (GEP) tests, donor derived serum cell-free DNA (e.g., dd-cfDNA) testing, breath testing and urine- based testing evaluation are possible ways to monitor organ transplant rejection.

Patients

The relevant population of interest is individuals who have received a solid organ transplant.

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Interventions
Using gene expression profiling (GEP) tests, donor derived serum cell-free DNA (e.g., dd-cfDNA) testing, breath testing and urine- based testing to determine prognosis and/or predict acute cellular rejection.

Comparators
Comparators of interest include organ biopsy to confirm a clinical suspicion of allograft rejection.

Outcomes
The general outcome interest is overall survival (OS), test validity, morbid events and hospitalizations. Follow-up over months to years is needed to monitor for signs of allograft rejection.

Heart Transplant Rejection
Most cardiac transplant recipients experience at least a single episode of rejection in the first year after transplantation. The International Society for Heart and Lung Transplantation modified is grading scheme for categorizing cardiac allograft rejection. The Revised (R) categories are listed in the below table:

New Grade	Definition	Old Grade
0R	No rejection	
1R	Mild rejection	1A, 1A and 2
2R	Moderate rejection	3A
3R	Severe rejection	3B and 4

Acute cellular rejection is most likely to occur in the first 6 months after transplantation, with a significant decline in the incidence of rejection after this time. Although immunosuppressants are required on a life-long basis, dosing is adjusted based on graft function and the grade of acute cellular rejection determined by histopathology. Endomyocardial biopsies are typically taken from the right ventricle via the jugular vein periodically during the first 6 to 12 months posttransplant. The interval between biopsies varies among clinical centers. A typical schedule is weekly for the first month, once or twice monthly for the following 6 months, and several times (monthly to quarterly) between 6 months and 1- year posttransplant. Surveillance biopsies may also be performed after the first postoperative year (e.g., on a quarterly or semiannual basis). This practice, although common, has not been demonstrated to improve transplant outcomes. Some centers no longer routinely perform endomyocardial biopsies after 1 year in individuals who are clinically stable.

While the endomyocardial biopsy is the criterion standard for assessing heart transplant rejection, it is limited by a high degree of interobserver variability in the grading of results and potential morbidity that can occur with the biopsy procedure. Also, the severity of rejection may not always coincide with the grading of the rejection by biopsy. Finally, a biopsy cannot be used to identify individuals at risk of rejection, limiting the

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ability to initiate therapy to interrupt the development of rejection. For these reasons, an endomyocardial biopsy is considered a flawed criterion standard by many. Therefore, noninvasive methods of detecting cellular rejection have been explored. It is hoped that noninvasive tests will assist in determining appropriate individual management and avoid overuse or underuse of treatment with steroids and other immunosuppressants that can occur with false-negative and false-positive biopsy reports.

Gene expression profiling (GEP) of mononuclear cells in peripheral blood specimens has been studied as an alternative to endomyocardial biopsy (EMB) to detect cellular rejection and is used to limit the number of surveillance biopsies. AlloMap gene expression assay (GEP) based on the literature was found to distinguish grade 0 (termed "quiescence") from moderate to severe rejection (grade ≥3 A in the 1990 system; classified as ≥2 R in the 2004 system). The test correctly identified 84% of moderate to severe rejection. Individuals with a score <30 at more than one-year posttransplant were highly unlikely to have moderate to severe rejection (negative predictive value 99.6 percent). This assay has been adopted clinically by many cardiac transplant programs.

Summary of Evidence
The recommendation for AlloMap is based on the results of the CARGO and IMAGE trials. The current International Society of Heart and Lung Transplantation (ISHLT) recommendations for the use of AlloMap in limited clinical protocols are the results of the IMAGE trial, and input from the transplant practice community supporting the use of AlloMap to assess risk for acute cellular rejection (ACR) in clinically stable heart transplant recipients. The evidence is sufficient to determine the effects of the technology on net health outcomes.

Noninvasive laboratory testing using gene expression profiling (GEP) (nCounter Human Organ Transplant Panel, MMDX Heart, breath testing (Heartsbreath), and donor derived cell-free DNA (dd-cfDNA) testing (MyTAIHeart Tests) to aid in the diagnosis of heart transplant rejection have been developed and studied, however, further evidence will be needed to determine the utility of these molecular diagnostic assay as a replacement for routine biopsies and other aspects of long-term management of heart transplant recipients. The evidence is insufficient to determine the effects of the technology on net health outcomes

Liver Transplant Rejection
Acute liver allograft rejection is an important cause of allograft dysfunction. Acute rejection episodes can have an impact on long-term graft survival, even among individuals who recover. The use of potent immunosuppressive agents for induction and maintenance therapy for liver transplantation has reduced the incidence of acute rejection, which is defined as liver allograft dysfunction associated with specific pathologic changes in the graft.

Acute rejection can be categorized into T- cell mediated (cellular) rejection (TCMR) and antibody-mediated (previously known as humoral) rejection. However, antibody-

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mediated rejection rarely occurs in liver transplantation recipients, while acute TCMR has been commonly reported. Acute T-cell mediated (cellular) rejection (TCMR) has been reported in approximately 10 to 30 percent of liver transplantation recipients.

Most episodes of acute T-cell mediated (cellular) rejection (TCMR) occur within three to six months after liver transplantation, although some episodes occur beyond six months. In addition, acute rejection after 12 months post-transplant is typically related to medication noncompliance, reduction in immunosuppression, or other factors interfering with calcineurin inhibitor trough levels (e.g., drug-drug interaction).

Most individuals who have acute TCMR are asymptomatic. However, some individuals present with fever, malaise, abdominal pain, hepatosplenomegaly, and rarely, increasing ascites. Because most individuals are asymptomatic, acute TCMR is suspected primarily by an increase in liver biochemical tests which may include elevations of any of the following: serum aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin levels. For individuals with suspected acute TCMR, further evaluation is typically performed within one week and includes:

- Liver allograft biopsy
- Liver ultrasound with Doppler study to exclude biliary strictures or vascular thrombosis (hepatic artery and portal vein)

The diagnosis of acute TCMR is made by examining liver allograft histology. The liver biopsy specimen is used for grading the severity of rejection and excluding other causes of elevated liver biochemical tests. A classification system for acute TCMR was developed by a panel of expert hepatologists who agreed on a nomenclature and histopathologic criteria for grading acute rejection i.e., Banff classification.

Summary of Evidence
Noninvasive laboratory testing using gene expression profiling (GEP) (e.g., nCounter Human Organ Transplant Panel) to aid in the diagnosis of liver transplant rejection have been developed and studied, however, further evidence will be needed to determine the utility of this molecular diagnostic assay as a replacement for routine liver biopsies and other aspects of long-term management of liver transplant recipients. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Lung Transplant Rejection
Acute allograft rejection is a significant problem in lung transplantation. Despite advances in induction immunosuppression and use of aggressive maintenance immunosuppression, more than a third of lung transplant recipients are treated for acute rejection in the first year after transplant. Acute rejection is responsible for approximately 4 percent of deaths in the first 30 days following transplantation.

Laboratory testing in individuals with suspected acute lung transplant rejection is generally nonspecific. Peripheral eosinophilia may be present; however, specific blood

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markers for rejection are not available. As infection is in the differential diagnosis, microbiologic stains and cultures are obtained from sputum, and bronchoalveolar lavage or bronchial washing samples. Cytomegalovirus (CMV) viral load testing is performed on peripheral blood.

The diagnosis of acute cellular rejection in lung transplant recipients is based on the presence of characteristic histopathologic changes on transbronchial lung biopsy specimens and exclusion of infection. Transbronchial lung biopsies need to be interpreted by a pathologist with experience in lung transplantation. For a symptomatic induvial, additional support for a diagnosis of acute cellular rejection includes the absence of airway stenosis at the time of flexible bronchoscopy and confirmation of negative microbiologic assays, stains, and cultures.

Clinical assessment without transbronchial biopsy is frequently inaccurate, as noted in a study from an experienced center in which only a 54 percent concordance rate was found between the clinical impression and the final pathologic diagnosis. Transbronchial lung biopsies improve the yield for a specific diagnosis to approximately 70 percent.
If the transbronchial biopsy does not yield a specific diagnosis and the individual has progressive respiratory impairment, repeat transbronchial biopsy, a video-assisted thoracoscopic lung biopsy, or, in the setting of acute lung injury, empiric therapy may be needed.

Summary of Evidence
Noninvasive laboratory testing using gene expression profiling (GEP) (e.g., nCounter Human Organ Transplant Panel, Molecular Microscopic Diagnostic System [MMDX)] lung) and donor derived cell-free DNA testing (Allosure Lung) to aid in the diagnosis of lung transplant rejection have been developed and studied, however, further evidence will be needed to determine the utility of these molecular diagnostic assay as a replacement for routine lung biopsies and other aspects of long-term management of lung transplant recipients. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Renal Transplant Rejection
Allograft dysfunction is typically asymptomatic and has a broad differential, including graft rejection. Diagnosis and rapid treatment are recommended to preserve graft function and prevent loss of the transplanted organ. For a primary kidney transplant, graft survival at 1 year is 94.7%; at 5 years, graft survival is 78.6%.

Surveillance of transplant kidney function relies on routine monitoring of serum creatinine, urine protein levels, and urinalysis. Allograft dysfunction may also be demonstrated by a drop in urine output or, rarely, as pain over the transplant site. With clinical suspicion of allograft dysfunction, additional noninvasive workup including ultrasonography or radionuclide imaging may be used. A renal biopsy allows a definitive assessment of graft dysfunction and is typically a percutaneous procedure performed with ultrasonography or computed tomography guidance. Biopsy of a transplanted kidney is

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associated with fewer complications than biopsy of a native kidney because the allograft is typically transplanted more superficially than a native kidney. Renal biopsy is a low-risk invasive procedure that may result in bleeding complications; loss of a renal transplant, as a complication of renal biopsy, is rare. Kidney biopsies allow for diagnosis of acute and chronic graft rejection, which may be graded using the Banff Classification. Pathologic assessment of biopsies demonstrating acute rejection allows clinicians to further distinguish between acute cellular rejection and antibody-mediated rejection, which are treated differently.

Summary of Evidence

Noninvasive laboratory testing using gene expression profiling (GEP) (nCounter Human Organ Transplant Panel, Kidney Solid Organ Response Tests [kSORT, TruGraf, Molecular Microscopic Diagnostic System [MMDX)] kidney, Clarava, and Tuteva), donor derived cell-free DNA testing (Allosure Kidney, Prospear, Viracor TRAC) and urine-based test (QiSant also known as QSant) to aid in the diagnosis of kidney transplant rejection have been developed and studied, however, further evidence will be needed to determine the utility of these molecular diagnostic assay as a replacement for routine kidney biopsies and other aspects of long-term management of kidney transplant recipients. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation

(2013) These joint guidelines by the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation provided guidance on the long-term management of liver transplants. There recommendations concerning assess of rejection are as follows:

- Rejection can be reliable diagnosed only on the basis of liver histology; a biopsy same should be taken before treatment initiation and classified according to the Banff criteria.
- Both forms of rejection are, until late stages, asymptomatic and the diagnosis is made through the investigation of abnormal liver tests; the diagnosis can be confirmed only on the basis of histology.

(*Accessed April 2022*)

European Association of Urology (EAU)

(2020) The European Association of Urology (EAU) published guidelines on renal transplantation, which states the following: "The ultimate standard for the diagnosis of rejection is transplant biopsy, because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g., acute tubular necrosis, infection, disease recurrence or CNI nephrotoxicity. Therefore, all rejections should be verified by renal biopsy." (*Accessed April 2022*)

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International Society of Heart and Lung Transplantation (ISHLT)
(2016) The International Society of Heart and Lung Transplantation (ISHLT) issued a guideline discussing antibody-mediated rejection (AMR) of the lung, the ISHT noted the following information:

- Lack of specific diagnostic criteria for AMR and listed allograft dysfunction, positive histology, post C4d staining, and donor-specific anti-human leukocyte antigen (HLA) antibodies (DSA) as potential diagnostic items for AMR.

(*Accessed April 2022*)

(2010) The International Society of Heart and Lung Transplantation (ISHLT) issued guidelines for the care of heart transplant recipients which included the following information:

- The standard of care for adult heart transplant recipients is to perform periodic endomyocardial biopsy (EMB) during the first 6-12 months after transplant for rejection surveillance.
- After the first-year post-transplant, EMB surveillance every 4-6 months is recommended in heart transplant patients at higher- risk of late acute rejection.
- Gene expression profiling using the AlloMap test can be used to rule out acute heart rejection (ACR) of grade 2R or greater in appropriate low- risk patients between 6 months and 5 years post heart transplant.

(*Accessed April 2022*)

Renal Association (RA)
(2017) The Renal Association (RA) published guidelines regarding post-operative care for individuals who received a kidney transplant. These guidelines have been endorsed by the British Transplant Society (BTS). The assessment of the rejection recommendations is listed below:

- We recommend that a transplant renal biopsy should be carried out before treating an acute rejection episode unless this will substantially delay treatment or pose a significant risk to the patient.
- We recommendation that a protocol transplant renal biopsy, defined as a biopsy performed in a stable graft without clinical evidence of acute rejection, be considered in the setting of persisting delayed graft function.

In the rationale, the Renal Association states: "Rejection episodes are characteristically associated with loss of graft function, but diagnosis is best established by a percutaneous biopsy since it differentiates rejection clearly from other causes of graft dysfunction." (*Accessed April 2022*)

Regulatory Status
The U.S. Food and Drug Administration (FDA) has cleared multiple biomarker tests for detection of cardiac and renal allograft rejection.

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Additionally clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high complexity testing.

The table below provides some of the testing currently included in this policy that have FDA or CLIA clearance. *The table below is not intended to be all inclusive*.

Test	Manufacturer	Clearance Date, Type & Number	Additional Information
AlloMap® Molecular Expression Testing	CareDx, formerly XDx	2008, 510(k), K073482	The test is to be used in conjunction with clinical assessment, for aiding in the identification of heart transplant recipients with stable allograft function and a low probability of moderate-to-severe transplant rejection. It is intended for individuals at least 15 years old who are at least 2 months posttransplant. *Specific criteria to define "low risk" have not been established. However, experts agree the test should not be performed in individuals who are at high risk for ACR or graft failure.*
AlloSure®	CareDx	dd-cfDNA	Commercially available laboratory-developed biomarker tests for detection of heart and renal allograft rejection. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. AlloSure is regulated under the CLIA standards, and all testing is performed at the CareDx reference laboratory.
Clarava™	Verici$_{DX}$	2022	Clarava is a pre-transplant, peripheral blood, prognosis test for

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			the risk of early acute rejection for kidney transplants using RNA expression by select transcriptome sequencing.
Heartsbreath ™	Menssana Research	2004, Humanitarian device exemption, H030004	To aid in diagnosing grade 3 heart transplant rejection in individuals who have received heart transplants within the preceding year. The device is intended as an adjunct to, and not as a substitute for, endomyocardial biopsy and is also limited to individuals who have had endomyocardial biopsy within the previous month.
MMDx® Heart	Kashi Clinical Laboratories	Tissue-based microarray	Tissue-based microarray mRNA gene expression test of 1283 genes post-transplant to provide a probability score of rejection as a complement to conventional biopsy processing. The test is not marketed to provide information for the diagnosis, prevention, or treatment of disease or to aid in the clinical decision-making process.
MMDx® Kidney	Kashi Clinical Laboratories	Tissue-based microarray	Tissue-based microarray mRNA gene expression test of 1494 genes post-transplant to provide a probability score of rejection as a complement to conventional biopsy processing. The test is not marketed to provide information for the diagnosis, prevention, or treatment of disease or to aid in the clinical decision-making process.
myTAI$_{HEART}$	TAI Diagnostics	dd-cfDNA	A laboratory developed test (LDT) developed for clinical diagnostic performance exclusively in the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendment (CLIA) accredited TAI Diagnostics Clinical Reference Laboratory.
Tuteva^{TM}	Verici$_{DX}$	2022	Tuteva is a post-transplant, peripheral blood, prognosis upon acute cellular rejection for kidney

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			transplant recipeints, including sub-clinical rejection as correlates to histopathology findings by using RNA expression by select transcriptome sequencing.
Viracor TRAC®	Eurofins	dd-cfDNA	To aid in the diagnosis of solid organ transplant rejection via NGS analysis. The fraction of dd-cfDNA is reported.

PRIOR APPROVAL

Not applicable.

POLICY

AlloMap Gene Expression Profiling (GEP) (81595)

- **AlloMap Gene Expression Profiling (GEP)**
  AlloMap gene expression profiling (GEP) may be considered **medically necessary** as a non-invasive method of determining the risk of rejection in heart transplant recipients ≥ 15 years of age, who are between six months through five years post heart transplant.
- **AlloMap Gene Expression Profiling (GEP)**
  AlloMap gene expression profiling (GEP) is considered **investigational** for heart transplant recipients when the above criteria has not been met and for all other indications because the evidence is insufficient to determine the effects of the technology on net health outcomes.

Gene Expression Profiling (GEP): Investigational

Gene expression profiling (GEP), including, but not limited to the following tests used to aid in the diagnosis of transplant rejection is considered **investigational**, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- Clarava
- Kidney Solid Organ Response Tests (kSORT)
- Molecular Microscopic Diagnostic System (MMDx) Heart
- Molecular Microscopic Diagnostic System (MMDx) Kidney
- Molecular Microscopic Diagnostic System (MMDx) Lung
- nCounter Human Organ Transplant Panel
- TruGraf Blood Gene Expression Test
- Tuteva

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Investigational
Testing used to aid in the diagnosis of transplant rejection including but are not limited to the following, are considered **investigational**, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- Breath Testing
  - Heartsbreath
- Donor Derived Cell-Free DNA (dd-cfDNA) Tests
  - Allosure Heart
  - Allosure Kidney
  - Allosure Lung
  - $MyTAI_{Heart}$ Test
  - Prospera
  - Viracor TRAC
- Urine-Based Tests
  - QiSant (e.g., QSant)

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0055U Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma (*when specified for MyTAIHeart*)
- 0087U Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score (*when specified for MMDX Heart*)
- 0088U Transplantation medicine (kidney allograft rejection), microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection (*when specified for MMDX Kidney*)
- 0118U Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA (*when specified for Viacor TRAC*)
- 0319U Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection (*when specified for Clarava™*)
- 0320U Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection (*when specified for Tuteva™)*
- 81479 Unlisted molecular pathology procedure (*when specified for one of the following: Allosure Heart, Allosure Kidney, Allosure Lung, MMDX Lung, Kidney*

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Solid Organ Response Test (ksort), nCounter Human Organ Transplant Panel, Prospera, QiSant (also known as Qsant), TruGraf Blood Gene Expression Test)

- 81595 Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing sub-fraction of peripheral blood, algorithm reported as a rejection risk score (*when specified for AlloMap*)
- 81599 Unlisted multianalyte assay with algorithmic analysis (*when specified for one of the following: Allosure Heart, Allosure Kidney, Allosure Lung, MMDX Lung, Kidney Solid Organ Response Test (ksort), nCounter Human Organ Transplant Panel, Prospera, QiSant (also known as Qsant), TruGraf Blood Gene Expression Test*)
- 84999 Unlisted chemistry procedure (*when specified for Heartsbreath Test*)
- 86849 Unlisted immunology procedure (*when specified for one of the following: Allosure Heart, Allosure Kidney, Allosure Lung, MMDX Lung, Kidney Solid Organ Response Test (ksort), nCounter Human Organ Transplant Panel, Prospera, QiSant (also known as Qsant), TruGraf Blood Gene Expression Test*)

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POLICY HISTORY

Date	Reason	Action
May 2022	Annual Review	Policy Revised
May 2021	Annual Review	Policy Revised
May 2020	Annual Review	Policy Revised
May 2019		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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