

Subject:	Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection	Publish Date:	07/07/2021 04/07/2021
Document #:	TRANS.00025	Last Review Date:	05/13/2021
Status:	Revised		

Description/Scope

This document addresses ~~multiple specific~~ noninvasive laboratory tests for the early detection of rejection following a heart transplant. This includes the Heartsbreath test (Menssana Research, Inc. Fort Lee, NJ), which measures the chemical byproducts of allograft rejection and has been investigated to potentially make the process of monitoring heart transplant recipients safer and less complicated. Also addressed in this document is the AlloMap[®] molecular expression testing (CareDx[®], Inc., Brisbane, CA) which has also been investigated as a noninvasive method of determining the risk of rejection in heart transplant recipients. [Additional tests include AlloSure[®] Heart, myTAI_{HEART} cell free DNA \(cfDNA\), MMDx Heart and others.](#)

Even with modern drug therapy, rejection remains a constant hazard, and transplant recipients must be tested repeatedly for signs of renewed rejection. Currently, the gold standard to detect heart transplant rejection is endomyocardial biopsy. This is typically performed weekly for the first 6 weeks, biweekly until the third month, monthly to 6 months and then every 1 to 3 months, as indicated.

Position Statement

Medically Necessary:

AlloMap molecular expression testing is considered **medically necessary** as a non-invasive method of determining the risk of rejection in heart transplant recipients between 1 and 5 years post-transplant.

Investigational and Not Medically Necessary:

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

~~No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.~~

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

Breath testing with the Heartsbreath test is considered **investigational and not medically necessary** for use as an aid in the diagnosis of heart transplant rejection.

AlloMap molecular expression testing is considered **investigational and not medically necessary** when the criteria above are not met.

[Additional noninvasive tests for detection of heart transplant rejection are considered **investigational and not medically necessary** including, but not limited, to AlloSure Heart, AlloSeq cell-free DNA, MMDx Heart and myTAI_{Heart}.](#)

Rationale

Breath Test

Heartsbreath (Breath test for Grade 3 heart transplant rejection), manufactured by Menssana Research, Inc., (Fort Lee, NJ) received U.S. Food and Drug Administration (FDA) clearance on February 24, 2004 under the Humanitarian Device Exemption (HDE)* program with the following indications for use:

The Heartsbreath test is indicated for use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The Heartsbreath test is intended for use as an adjunct to, and not as a substitute for, endomyocardial biopsy. The use of the device is limited to patients who have had endomyocardial biopsy (EMB) within the previous month (FDA, 2004).

The Heartsbreath test works on the principle that rejection of the transplanted heart is accompanied by oxidative stress that degrades membrane polyunsaturated fatty acids, evolving alkanes and methylalkanes that are excreted in the breath as volatile organic compounds (VOCs). The individual breathes for 2 minutes through a disposable mouthpiece attached to a breath collecting device, which then analyzes the VOCs in alveolar and room air and interprets the values, using a proprietary algorithm to predict the probability of Grade 3 heart transplant (HT) rejection.

The Heartsbreath test should not be used for individuals who have received an HT more than 1 year ago, or have a Grade 4 HT rejection, because Heartsbreath has not been evaluated in these groups.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

FDA clearance was based on the results of the Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (HARDBALL) Study, which was sponsored by the National Heart Lung and Blood Institute (NHLBI). In this 3-year multicenter study, investigators evaluated a new marker of HT rejection, the breath methylated alkane contour (BMAC). In the HARDBALL study, 1061 breath VOC samples were collected from 539 HT recipients at seven sites on the day of scheduled EMB. The gold standard of rejection was the concordant set of International Society for Heart and Lung Transplantation (ISHLT) grades in biopsies read by two cardiac pathologists. Results included concordant biopsies of:

- Grade 0, 645 of 1061 (60.8%);
- Grade 1A, 197 (18.6%);
- Grade 1B, 84 (7.9%);
- Grade 2, 93 (8.8%);
- Grade 3A, 42 (4.0%).

A combination of 9 VOCs in the BMAC identified Grade 3 rejection (sensitivity 78.6%; specificity 62.4%; cross-validated sensitivity 59.5%; cross-validated specificity 58.8%; positive predictive value [PPV] 5.6%; negative predictive value [NPV] 97.2%). Site pathologists identified the same cases with sensitivity of 42.4%, specificity 97.0%, PPV 45.2% and NPV 96.7%. The authors concluded that a breath test for markers of oxidative stress was more sensitive and less specific for Grade 3 HT rejection than a biopsy reading by a single on-site pathologist, but the NPV of the two tests were similar. They concluded that a negative screening breath test could potentially identify transplant recipients at low risk of Grade 3 rejection and obviate the need for EMB in this group, thereby reducing the overall number of EMBs performed, which was estimated to be by as much as 50% (Phillips, 2004).

Currently, there is inadequate evidence in the published literature to demonstrate the safety, efficacy, and clinical utility of the Heartsbreath test in the management of rejection surveillance following HT. Large trials are needed to further define the role of this technology and demonstrate how use of this test will impact treatment management.

AlloMap Molecular Expression Testing

The AlloMap molecular expression blood test was developed by XDx, Inc. (South San Francisco, CA), now known as CareDx, Inc., (Brisbane, CA). In 2008, FDA 510(k) clearance as a Class II approval was granted for AlloMap Molecular Expression Testing (CareDx, Inc., Brisbane, CA) as an in-vitro, diagnostic, multivariate, index assay test

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

~~service, which assesses~~of the gene expression profile of RNA isolated from peripheral blood mononuclear cells for the following indication:

To aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection (ACR) at the time of testing in conjunction with standard clinical assessment. AlloMap is indicated for use in heart transplant recipients who are 15 years of age or older and at least 2 months (greater than or equal to 55 days) post-transplantation (FDA, 2008).

The test assesses the expression of 20 genes, about half of which are directly involved in rejection while the remainder provide other information needed for rejection risk assessment. It is hoped the results of this test will decrease the number of necessary [endomyocardial biopsies \(EMBs\)](#). Among the proposed benefits are the AlloMap test's ability to differentiate mild rejection, for which histologic findings may be the least accurate, and the potential for monitoring physiologic responses to steroid weaning. It has been recognized that the test is not effective at monitoring rejection within the first 6 months of transplantation, and it is yet unclear what a high AlloMap score might mean in the setting of no histologic rejection.

~~The Cardiac Allograft Rejection Gene Expression Observation Study (CARGO) investigated these patterns of gene expression, detected in peripheral blood by the AlloMap testing. CARGO, were studied in the Cardiac Allograft Rejection Gene Expression Observation Study (CARGO), which included eight U.S. cardiac transplant centers where and 650 heart transplant (HT) recipients were tested. Results of the CARGO study have appeared in abstracts presented at the 2005 annual meeting of the International Society for Heart and Lung Transplantation (ISHLT). While the results were promising, the data was/were considered inadequate to permit firm scientific conclusions regarding how use of this test will impact the management of HT recipients (Deng, 2006).~~

~~There have been s~~Subsequent validation studies and sub-study analyses of the CARGO results ~~which provided additional data regarding the potential utility of the AlloMap test in detecting transplant rejection (Bernstein, 2007; Mehra, 2007b; Mehra, 2008). More recent results of the CARGO and the CARGO II trial, a European based observational study to further validate the gene expression profiling (GEP) test performance of AlloMap, have been published with findings that reflect similar results. CARGO II was a European observational study to further validate AlloMap's gene expression profiling (GEP) test performance. For greater than or equal to 2-6 months and greater than 6 months post-transplantation, the CARGO II GEP score performance (AUC-ROC=0.70 and 0.69) is similar to the CARGO study results (AUC-ROC=0.71 and 0.67). It was the opinion of the t~~ Trial investigators

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

~~propose~~ that the low prevalence of ACR contributed to the high ~~negative predictive value (NPV)~~ and limited ~~positive predictive value (PPV)~~ of GEP testing. ~~The authors concluded that~~ They concluded that the choice of threshold score for the practical use of GEP testing with AlloMap should consider the overall clinical assessment of the individual's baseline risk for rejection (Crespo-Leiro, 2015; 2016).

~~Results of another trial were published in 2010.~~ The Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial ~~was published in 2010. This was a , which was a sponsored by the manufacturer of AlloMap (XDx, Inc.), was a randomized, event-driven, noninferiority trial sponsored by the manufacturer of AlloMap (XDx, Inc.) IMAGE which~~ was conducted at 13 U.S. transplant centers between January 2005 and October 2009 (with median follow-up of 19 months). This trial included 602 ~~selected~~ transplant recipients who had undergone a transplant more than 6 months prior and who were considered at low risk for rejection. The purpose of this study was to compare rejection outcomes between those who underwent routine EMB and those who were monitored with the AlloMap GEP test. The primary outcome was the first occurrence of rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or retransplantation. Results indicated that a ~~strategy of~~ monitoring for rejection ~~that involved with~~ GEP, as compared with routine biopsies, was not associated with an increased risk of serious adverse outcomes and resulted in the performance of significantly fewer biopsies. ~~During the median follow-up period (19 months), s~~Subjects who were monitored with AlloMap and those who underwent routine EMB had similar 2-year cumulative rates of the composite primary outcome (14.5% and 15.3%, respectively; hazard ratio [HR] with GEP, 1.04; 95% confidence interval [CI], 0.67 to 1.68). The 2-year rates of death from any cause were also similar in the two groups (6.3% and 5.5%, respectively; p=0.82). Although the limited power of the study did not allow for firm conclusions regarding the utility of AlloMap ~~as a substitute for EMB, the authors concluded that GEP of peripheral blood specimens may offer a reasonable alternative to routine EMB, for monitoring cardiac transplant rejection,~~ if the interval since transplantation is at least 6 months and the individual is considered to be at low risk for rejection (Pham, 2010).

In 2010, the ISHLT issued guidelines for the care of HT recipients which included the following:

- The standard of care for adult HT recipients is to perform periodic EMB during the first 6-12 months after transplant for rejection surveillance; (Class IIa, Level of Evidence: C)
- After the first year post-transplant, EMB surveillance every 4-6 months is recommended for patients at higher risk of late acute rejection; (Class IIa, Level of Evidence: C)

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

~~No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.~~

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

- GEP using the AlloMap test can be used to rule out the presence of ACR of grade 2R or greater in appropriate low-risk patients between 6 months and 5 years post-transplant (Class IIa, Level of Evidence: B) (Costanzo ISHLT, 2010).

Another 2010 portion of the ISHLT guideline titled, “Task Force 2: Immunosuppression and Rejection” noted the following regarding the grading scale for risk of ACR in HT recipients:

Due to intra- and interobserver variability in the determination of the different grades of mild or moderate rejection and the observation that grades 1 and 2 were mostly self-limited, a revised heart allograft rejection grading system was published in 2005 as follows (Stewart, 2005):

- Grade 0 (no cellular rejection) was now named grade 0R (‘R’ added to reflect the revised 2005 scale);
- The intermediate grades of 1A, 1B, and 2 were re-classified as grade 1R, or mild ACR;
- Grades 3A was re-classified as grade 2R, moderate ACR; and
- Grade 3B and 4 were re-classified as grade 3R, severe ACR.
- In addition, AMR (antibody mediated rejection) was recognized as a clinical entity, and recommendation was issued for determination of its presence (AMR1) or absence (AMR0) (Taylor ISHLT, 2010).

~~The recommendation for AlloMap is based on the results of the CARGO and IMAGE trials (Costanzo, 2010).~~

~~In summary, the eCurrent ISHLT recommendations for the use of AlloMap in limited clinical protocols are reflect the results of the IMAGE trial, and iInput from the transplant practice community supports the use of AlloMap to assess risk for ACR in clinically stable HT recipients between 1 and 5 years post-transplant.~~

Breath testing

Heartsbreath (Breath test for Grade 3 heart transplant rejection), manufactured by Menssana Research, Inc., (Fort Lee, NJ) received U.S. Food and Drug Administration (FDA) clearance on February 24, 2004 under the Humanitarian Device Exemption (HDE)* program with the following indications for use:

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

~~No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.~~

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

The Heartsbreath test is indicated for use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The Heartsbreath test is intended for use as an adjunct to, and not as a substitute for, endomyocardial biopsy. The use of the device is limited to patients who have had endomyocardial biopsy (EMB) within the previous month (FDA, 2004).

The Heartsbreath test works on the principle that rejection of the transplanted heart is accompanied by oxidative stress that degrades membrane polyunsaturated fatty acids, generating alkanes and methylalkanes that are excreted in the breath as volatile organic compounds (VOCs). The individual breathes for 2 minutes through a disposable mouthpiece attached to a breath collecting device. The device then analyzes the VOCs in alveolar and room air and uses a proprietary algorithm to predict the probability of Grade 3 HT rejection.

The Heartsbreath test should not be used for individuals who have received an HT more than 1 year ago, or for those who have a Grade 4 HT rejection, because Heartsbreath has not been evaluated in these groups.

FDA clearance was based on the results of the Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (HARDBALL) Study sponsored by the National Heart Lung and Blood Institute (NHLBI). In this 3-year multicenter study, investigators evaluated a new marker of HT rejection, the breath methylated alkane contour (BMAC). In the HARDBALL study, 1061 breath VOC samples were collected from 539 HT recipients at seven sites on the day of scheduled EMB. The gold standard of rejection was the concordant set of ISHLT grades in biopsies read by two cardiac pathologists. Results included concordant biopsies of:

- Grade 0, 645 of 1061 (60.8%);
- Grade 1A, 197 (18.6%);
- Grade 1B, 84 (7.9%);
- Grade 2, 93 (8.8%);
- Grade 3A, 42 (4.0%).

A combination of 9 VOCs in the BMAC identified Grade 3 rejection (sensitivity 78.6%; specificity 62.4%; cross-validated sensitivity 59.5%; cross-validated specificity 58.8%; PPV 5.6%; NPV 97.2%). Site pathologists identified the same cases with sensitivity of 42.4%, specificity 97.0%, PPV 45.2% and NPV 96.7%. The authors concluded that a breath test for markers of oxidative stress was more sensitive and less specific for Grade 3 HT rejection than a biopsy reading by a single on-site pathologist, but the NPV of the two tests were similar. They concluded that a negative screening breath test could potentially identify transplant recipients at low risk of Grade 3 rejection and

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

~~No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.~~

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

obviate the need for EMB in this group, thereby reducing the overall number of EMBs performed, which was estimated to be by as much as 50% (Phillips, 2004).

Currently, there is inadequate evidence in the published literature to demonstrate the safety, efficacy, and clinical utility of the Heartsbreath test in the management of rejection surveillance following HT. Large trials are needed to further define the role of this technology and demonstrate how use of this test will impact treatment management.

AlloSure Heart and other donor-derived cell free DNA (dd-cfDNA)

Elevated levels of donor-derived cell free DNA (dd-cfDNA) are shed from the donor graft and associated with transplanted organ injury and rejection (Grskovic, 2016; Khush, 2019). The AlloSure Heart test (CareDx, Inc. Brisbane, CA) has been promoted as a noninvasive alternative to EMB as early as 14 days post transplant. This is a next generation sequencing (NGS)-based assay that quantifies dd-cfDNA relative to the total amount of cfDNA derived from a plasma sample. It uses single-nucleotide polymorphisms (SNPs) to quantify dd-cfDNA in transplant recipients without requiring separate genotyping of the donor and recipient. Test results represent the percent of dd-cfDNA in the total cfDNA in a heart transplant recipient. Changes in the percentage of dd-cfDNA over time provide further evaluation for HT rejection. This plasma test is only performed at a single CareDx CLIA laboratory. Results are expected to be reported within 3 days of blood draw. Early studies have consistently shown a correlation between elevated levels of cfDNA and organ rejection or cellular graft injury (Macher, 2019).

Clinical validity was investigated in two observational prospective studies, the Utility of Donor-Derived Cell Free DNA in Association with Gene Expression Profiling (D-OAR; NCT02178943) and the Cedars-Sinai single-center study. The D-OAR trial included 740 HT recipients at 26 transplant centers in the U.S. Plasma dd-cfDNA was quantified by using targeted amplification and sequencing of a single nucleotide polymorphism panel. The dd-cfDNA levels were correlated to paired events of biopsy-based diagnosis of rejection. The median dd-cfDNA was 0.07% in reference HT recipients (2164 samples) and 0.17% in samples classified as acute rejection (35 samples; p=.005). At a 0.2% threshold, dd-cfDNA had a 44% sensitivity to detect rejection and a 97% NPV. The Cedars-Sinai cohort study of 33 HT recipients considered at high risk for antibody-mediated rejection (AMR) found dd-cfDNA levels were elevated 3-fold in AMR compared with patients without AMR (99 samples; p=.004). The authors concluded that reported test performance characteristics will guide the next stage of clinical utility studies of the dd-cfDNA assay (Khush, 2019).

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

[Knight and colleagues conducted a systematic review of the literature for the use of cfDNA in monitoring of graft health after solid organ transplant \(SOT\). Electronic databases were searched for studies relating cfDNA fraction or levels to clinical outcomes, and data including measures of diagnostic test accuracy were extracted. Narrative analysis was performed. Ninety-five articles from 47 studies met the inclusion criteria \(18 kidneys, 7 livers, 11 hearts, 1 kidney-pancreas, 5 lungs, and 5 multiorgans\). The majority were retrospective and prospective cohort studies, with 19 reporting diagnostic test accuracy data. Multiple techniques for measuring dd-cfDNA were reported, including many not requiring a donor sample. It was noted that dd-cfDNA falls rapidly within 2 weeks post transplant and that baseline levels vary by organ type. Levels are elevated in the presence of allograft injury, including acute rejection and infection and return to baseline after successful treatment. Elevation of cfDNA levels is seen in advance of clinically apparent organ injury. Discriminatory power was greatest for higher grades of T cell-mediated and antibody-mediated acute rejection, with high NPVs. The authors noted that cfDNA is a promising biomarker for monitoring the health of SOTs. Future study is needed to define clinical utility and benefit in routine prospective monitoring following SOT \(Knight, 2019\).](#)

[The myTAI_{HEART} \(TAI Diagnostics, Inc., Milwaukee, WI\) is another laboratory-developed test that measures dd-cfDNA in blood plasma as a marker for ACR and transplanted organ injury. This test is conducted exclusively at the TAI Diagnostics clinical reference laboratory with proprietary software using quantitative PCR genotyping to predict risk for ACR. It is proposed for use in HT recipients 2 months of age or older at least 1 week post HT \(TAI, 2018\). To date, observational studies with small sample size have suggested that dd-cfDNA monitoring of HT recipients may be a useful tool to detect and probably anticipate ACR \(North, 2020\). Further study is needed to inform about how test results should be interpreted in the context of the individual's total clinical findings, history and other test results. TAI Diagnostics reported temporary suspension of production of the myTAI_{HEART} test in 2020. Production has not resumed at the time of this update.](#)

[Additional non-invasive tests](#)

[AlloSeq[®] cfDNA \(CareDx Inc, Brisbane, CA\) also measures dd-cfDNA utilizing low DNA input, NGS technology, and streamlined analysis to assist in improved transplant surveillance. To date, this test is being used for research purposes only.](#)

[The Presage[®] ST₂ assay \(soluble suppression of tumorigenicity-2\) \(Critical Diagnostics, San Diego, CA\) in serum is another noninvasive test which has been cleared by the FDA for use in the prognostic evaluation of chronic heart](#)

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

failure (HF). It has also been suggested for use as a prognostic biomarker post HT as a predictor of AMR (graft-versus-host disease). To date, published evidence has been limited to a few retrospective observational studies. Large well designed trials are needed (Januzzi, 2013; Pascual-Figal, 2011).

The Molecular Microscope® MMDx—Heart (Kashi Clinical Laboratories, Portland, OR) is a microarray-based system that utilizes microRNA profiling (mRNA gene expression analysis) to assess EMB specimens following HT. It is proposed for use in prognostic evaluations for AMR. Further validation is needed in large well designed trials to confirm initial favorable findings (Halloran, 2017).

The Viracor TRAC® Heart dd-cfDNA (Viracor Eurofins, Inc. Lee’s Summit, MO) is another assay that uses NGS to determine the percentage of circulating cfDNA in transplant recipients. The cfDNA is extracted from plasma isolated from whole blood. NGS and genome-wide recipient genotype data are then analyzed by a bioinformatics pipeline that calculates the percentage of dd-cfDNA present. This is proposed to correlate with allograft injury due to rejection. To date, this test has not been cleared for diagnostic use by the FDA. This test is not suitable for use during pregnancy, if the donor and recipient are identical twins, if the individual has received multiple transplants from different donors, or if the donor and recipient are siblings from a consanguineous marriage. According to the manufacturer, these clinical situations will cause the bioinformatics pipeline to generate an inaccurate result.

In summary, published scientific information does not show that use of laboratory tests, other than AlloMap molecular profiling testing, leads to improved health outcomes in clinical practice.

Background/Overview

Breath Test

Although the current gold standard test for detecting rejection is EMB, this is limited in accuracy, has a high degree of inter-observer variability, and may yield tissue that is not representative of the overall pathology. It is also invasive and can lead to infections, arrhythmias, or ventricular perforation. Despite these limitations, the breath test is currently not established as a substitute for EMB.

According to a scientific statement about newer tests for HT rejection from the American Heart Association, the following is noted:

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

~~No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.~~

This Medical Policy provides assistance in understanding Healthy Blue’s standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue’s Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

Standardization of management strategies for AMR is lacking in large part because of the absence of clinical trials that prospectively evaluate therapies for AMR. The definition of AMR is also in flux as more sensitive diagnostic modalities become available. Although the currently available gene expression profile test for rejection (Allomap) is useful in the prediction of ACR, there is evidence that the fraction of circulating cell-free donor DNA may be useful in detecting both ACR and AMR (Colvin, 2015).

***Note:** A Humanitarian Use Device (HUD) is a device that has been given special approval by the FDA under the Humanitarian Device Exemption (HDE) regulations and is utilized in special circumstances where a condition is so rare (fewer than 4000 individuals in the U.S. per year) that testing of large numbers of subjects is not feasible. In these special situations, the FDA may grant an HDE provided that: the device does not pose an unreasonable or significant risk of illness or injury; and the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the FDA notes that the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market. The labeling for an HUD must state that the device is a Humanitarian Use Device and that, although the device is authorized by federal law, the effectiveness of the device for the specific indication has not been demonstrated- (FDA, 2004).

AlloMap Molecular Expression Testing

The California Technology Assessment Forum (CTAF) conducted a technology assessment of GEP for the diagnosis of HT rejection in 2006, at which time it was determined that the use of GEP did not meet CTAF criteria when used to manage HT patients. The CTAF assessment stated that:

Gene expression profiling offers the potential for a non-invasive test that may replace endomyocardial biopsy as the gold standard for transplant rejection. However, given the history of poor reproducibility of other gene expression profiles in the recent past, it is prudent to require independent confirmation of the CARGO study results before widespread adoption of the AlloMap gene expression profile to monitor heart transplant patients for early detection of rejection (CTAF, 2006).

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

~~No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.~~

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

This initial CTAF determination was based on concerns around the post hoc change in the threshold used to define a positive test result in the CARGO study and the small size of this primary validation study, in addition to the fact that there were no studies, published to date, comparing the clinical outcomes of individuals monitored with GEP to those monitored with EMB (CTAF, 2006).

In 2010, the CTAF conducted a systematic re-review of available published evidence focusing on results of the AlloMap test which included six observational studies and one randomized trial. Three of the publications included in this review reported on subsets of participants from the CARGO trial, as well as results of the IMAGE trial and concluded that, “This technology meets CTAF’s assessment criteria for safety, effectiveness and improvement in health outcomes when used to manage HT patients at least one year post transplant.” The CTAF assessment included the following conclusions:

The AlloMap gene expression profile has a high negative predictive value, but a low positive predictive value. Thus, it may be useful to avoid biopsy in stable patients, but the high false positive rate precludes its use to definitively diagnose acute cellular rejection. Endomyocardial biopsies will still need to be performed in all patients with elevated AlloMap scores and all patients with clinical signs of rejection. The IMAGE trial provides data supporting the non-inferiority of a monitoring strategy for heart transplant patients incorporating the AlloMap gene expression profile in lieu of routine endomyocardial biopsy. However, the data only support such strategies in patients more than a year post transplant. More data are needed to confirm the tests utility earlier in the post transplant period when the majority of endomyocardial biopsies are performed (CTAF/Tice, 2010).

In 2011, the Blue Cross Blue Shield Association published a Technology Assessment Report of GEP as a noninvasive method to monitor for cardiac allograft rejection. This review and analysis of the available published evidence concluded that the use of GEP as a noninvasive method to monitor for cardiac allograft rejection does not meet the TEC criteria. The following are some summarized conclusions:

Although a higher score is associated with a greater likelihood of rejection class 3A or higher, the diagnostic characteristics of AlloMap[®] testing are uncertain. Study methods are unclear, study samples are incompletely described, numbers of cases of rejection are apparently small, and cutoff scores appear to have been determined post hoc. The sensitivity of the test for detecting rejection is uncertain (TEC, 2011).

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue’s standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue’s Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

~~According to a scientific statement about newer tests for HT rejection from the American Heart Association, the following is noted:~~

~~Standardization of management strategies for AMR is lacking in large part because of the absence of clinical trials that prospectively evaluate therapies for AMR. The definition of AMR is also in flux as more sensitive diagnostic modalities become available. Although the currently available gene expression profile test for rejection (Allogmap) is useful in the prediction of ACR, there is evidence that the fraction of circulating cell-free donor DNA may be useful in detecting both ACR and AMR (Colvin, 2015).~~

Definitions

Allograft rejection, also referred to as acute cellular rejection (ACR): The recipient’s immune system rejects the donor heart.

Antibody-mediated rejection (AMR): Refers to all allograft rejection caused by antibodies directed against donor-specific HLA molecules, blood group antigen (ABO)-isoagglutinins, or endothelial cell antigens. Antibody-mediated rejection causes chronic graft failure which is typically resistant to therapy and carries an ominous prognosis for the graft.

Endomyocardium: The innermost lining of the heart.

Endomyocardial biopsy (EMB): A tissue sample of the endomyocardium.

Heart transplant (HT): Removal of a human heart and replacing it with a donor heart.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

~~No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.~~

This Medical Policy provides assistance in understanding Healthy Blue’s standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue’s Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

When services may be Medically Necessary when criteria are met:

CPT

81595 Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score AlloMap[®], CareDx, Inc.

ICD-10 Diagnosis

All diagnoses

When services are Investigational and Not Medically Necessary:

For the procedure code listed above when criteria are not met.

When services are also Investigational and Not Medically Necessary:

For the procedure codes listed below ~~in all instances~~, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

0055U Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma myTAIHEART, TAI Diagnostics, Inc, TAI Diagnostics, Inc

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

0118U Molecular Microscope[®] MMDx—Heart, Kashi Clinical Laboratories
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 heart transplant rejection]
Viracor TRAC[™] dd-cfDNA, Viracor Eurofins, Viracor Eurofins

81479 Unlisted molecular pathology procedure [when specified as testing for heart transplant rejection, such as Allosure Heart, AlloSeq cfDNA, Presage ST2]

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

81599	Unlisted multianalyte assay with algorithmic analysis [when specified as testing for heart transplant rejection]
84999	Unlisted chemistry procedure [when specified as breath test for heart transplant rejection (Heartsbreath test)]

ICD-10 Diagnosis

T86.20-T86.298	Complications of heart transplant
Z48.21	Encounter for aftercare following heart transplant
Z94.1	Heart transplant status
	All diagnoses

References

Peer Reviewed Publications:

1. [Agbor-Enoh S, Tunc I, De Vlamincq I, et al. Applying rigor and reproducibility standards to assay donor-derived cell-free DNA as a non-invasive method for detection of acute rejection and graft injury after heart transplantation. J Heart Lung Transplant. 2017; 36\(9\):1004-1012.](#)
- 1-2. [Bernstein D, Williams GE, Eisen H, et al. Gene expression profiling distinguishes a molecular signature for grade 1B mild acute cellular rejection in cardiac allograft recipients. J Heart Lung Transplant. 2007; 26\(12\):1270-1280.](#)
- 2-3. [Cadeiras M, Shahzad K, John MM, et al. Relationship between a validated molecular cardiac transplant rejection classifier and routine organ function parameters. Clin Transplant. 2010; 24\(3\):321-327.](#)
- 3-4. [Cadeiras, M, von Bayern M, Sinha A, et al. Noninvasive diagnosis of acute cardiac allograft rejection. Curr Opin Organ Transplant. 2007; 12\(5\):543-550.](#)
- 4-5. [Crespo-Leiro MG, Stypmann J, Schulz U, et al. Performance of gene-expression profiling test score variability to predict future clinical events in heart transplant recipients. BMC Cardiovasc Disord. 2015; 15:120.](#)
- 5-6. [Crespo-Leiro MG, Stypmann J, Schulz U, et al. Clinical usefulness of gene-expression profile to rule out acute rejection after heart transplantation: CARGO II. Eur Heart J. 2016; 37\(33\):2591-2601.](#)
- 6-7. [Crespo-Leiro MG, Zuckermann A, Bara C, et al. Concordance among pathologists in the second Cardiac Allograft Rejection Gene Expression Observational Study \(CARGO II\). Transplantation. 2012; 94\(11\):1172-1177.](#)

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

- 7-8. Deng MC, Eisen HJ, Mehra MR, et al.; CARGO Investigators. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant.* 2006; 6(1):150-160.
- 8-9. Deng MC, Elashoff B, Pham MX, et al.; IMAGE Study Group. Utility of gene expression profiling score variability to predict clinical events in heart transplant recipients. *Transplantation.* 2014; 97(6):708-714.
- 9-10. Fang KC. Clinical utilities of peripheral blood gene expression profiling in the management of cardiac transplant patients. *J Immunol.* 2007; 4(3):209-217.
- 10-11. Fujita B, Prashovikj E, Schulz U, et al. Predictive value of gene expression profiling for long-term survival after heart transplantation. *Transpl Immunol.* 2017; 41:27-31.
12. Grskovic M, Hiller DJ, Euban LA, et al. [Validation of a clinical-grade assay to measure donor-derived cell-free DNA in solid organ transplant recipients.](#) *J Mol Diagn.* 2016; 18(6):890-902.
13. Halloran PF, Potena L, Van Huyen JD, et al. [Building a tissue-based molecular diagnostic system in heart transplant rejection: The heart Molecular Microscope Diagnostic \(MMDx\) System.](#) *J Heart Lung Transplant.* 2017; 36(11):1192-1200.
14. Hidestrand M, Tomita-Mitchell A, Hidestrand PM, et al. [Highly sensitive non-invasive cardiac transplant rejection monitoring using targeted quantification of donor specific cell free DNA.](#) *J Am Coll Cardiol.* 2014; 63(12):1224-1226.
15. Januzzi JL, Horne BD, Moore SA, et al. [Interleukin receptor family member ST2 concentrations in patients following heart transplantation.](#) *Biomarkers.* 2013; 18(3):250-256.
- 14-16. Jarcho JA. Fear of rejection--monitoring the heart-transplant recipient. *N Engl J Med.* 2010; 362(20):1932-1933.
17. Khush KK, Patel J, Pinney S, et al. [Noninvasive detection of graft injury after heart transplant using donor-derived cell-free DNA: A prospective multicenter study.](#) *Am J Transplant.* 2019; 19:2889-2899.
18. Knight SR, Thorne A, Lo Faro ML. [Donor-specific cell-free DNA as a biomarker in solid organ transplantation. A systematic review.](#) *Transplant.* 2019; 103(2):273-283.
- 12-19. Kobashigawa J, Patel J, Azarbal B, et al. Randomized pilot trial of gene expression profiling versus heart biopsy in the first year after heart transplant: early invasive monitoring attenuation through gene expression trial (EIMAGE). *Circ Heart Fail.* 2015; 8(3):557-564.
- 13-20. Loupy A1, Duong Van Huyen JP2, et al. Gene expression profiling for the identification and classification of antibody-mediated heart rejection. *Circ.* 2017; 135(10):917-935.
21. Macher HC, García-Fernández N, Adsuar-Gómez A, et al. [Donor-specific circulating cell free DNA as a noninvasive biomarker of graft injury in heart transplantation.](#) *Clin Chim Acta.* 2019; 495:590-597.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

[14-22.](#) Marboe CC, Lal PG, Chu K, et al. Distinctive peripheral blood gene expression profiles in patients forming nodular endocardial infiltrates (Quilty lesions) following heart transplantation. *J Heart Lung Transplant.* 2005; 24(2 suppl):S97.

[15-23.](#) Mehra MR, Kobashigawa JA, Deng MC, et al.; CARGO Investigators. Transcriptional signals of T-cell and corticosteroid-sensitive genes are associated with future acute cellular rejection in cardiac allografts. *J Heart Lung Transplant.* 2007b; 26(12):1255-1263.

[16-24.](#) Mehra MR, Kobashigawa JA, Deng MC, et al.; CARGO Investigators. Clinical implications and longitudinal alteration of peripheral blood transcriptional signals indicative of future cardiac allograft rejection. *J Heart Lung Transplant.* 2008; 27(3):297-301.

[17-25.](#) Mehra MR, Uber PA. Genomic biomarkers and heart transplantation. *Heart Fail Clin.* 2007a; 3(1):83-86.

[26.](#) [North PE, Ziegler E, Mahnke DK, et al. Cell-free DNA donor fraction analysis in pediatric and adult heart transplant patients by multiplexed allele-specific quantitative PCR: Validation of a rapid and highly sensitive clinical test for stratification of rejection probability. *PLoS One.* 2020; 15\(1\).](#)

[27.](#) [Pascual-Figal DA, Garrido IP, Blanco R, et al. Soluble ST2 is a marker for acute cardiac allograft rejection. *Ann Thorac Surg.* 2011; 92\(6\): 2118-2124.](#)

[18-28.](#) Pham MX, Deng MC, Kfoury AG, et al. Molecular testing for long-term rejection surveillance in heart transplant recipients: design of the Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial. *J Heart Lung Transplant.* 2007; 26(8):808-814.

[19-29.](#) Pham MX, Teuteberg JJ, Kfoury AG, et al.; IMAGE Study Group. Gene-expression profiling for rejection surveillance after cardiac transplantation. *N Engl J Med.* 2010; 362(20):1890-1900.

[20-30.](#) Phillips M, Boehmer JP, Cataneo RN, et al. Heart allograft rejection: detection with breath alkanes in low levels (the HARDBALL study). *J Am Coll Cardiol.* 2002; 40(1):12-13.

[21-31.](#) Phillips M, Boehmer JP, Cataneo RN, et al. Heart allograft rejection: detection with breath alkanes in low levels (the HARDBALL study). *J Heart Lung Transplant.* 2004a; 23(6):701-708.

[22-32.](#) Phillips M, Boehmer JP, Cataneo RN, et al. Prediction of heart transplant rejection with a breath test for markers of oxidative stress. *Am J Cardiol.* 2004b; 94(12):1593-1594.

[33.](#) [Regalie W, Stamm K, Hidestrand P. Novel assay to calculate donor fraction of cell-free DNA in heart transplant. *J Am Coll Cardiol.* 2018; 71\(11\):supplement A764.](#)

[34.](#) [Regalie W, Stamm K, Mahnke D, et al. Noninvasive assay for donor fraction of cell-free DNA in pediatric heart transplant recipients. *J Am Coll Cardiol.* 2018; 71\(25\):2982-2983.](#)

[35.](#) [Richmond ME, Zangwill SD, Kindel SJ, et al. Donor fraction cell-free DNA and rejection in adult and pediatric heart transplantation. *J Heart Lung Transplant.* 2020; 39\(5\): 454-463.](#)

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

- 23-36. Sobotka PA, Gupta DK, Lansky DM, et al. Breath pentane is a marker of acute cardiac allograft rejection. *J Heart Lung Transplant.* 1994; 13(2):224-229.
- 24-37. Starling RC, Pham M, Valantine H, et al.; Working Group on Molecular Testing in Cardiac Transplantation. Molecular testing in the management of cardiac transplant recipients: initial clinical experience. *J Heart Lung Transplant.* 2006; 25(12):1389-1395.
- 25-38. Strecker T, Rösch J, Weyand M, Agaimy A. Endomyocardial biopsy for monitoring heart transplant patients: 11-years-experience at a German heart center. *Int J Clin Exp Pathol.* 2013; 6(1):55-65.
39. [Van Huyen JPD, Tible M, Gay A, et al. MicroRNAs as non-invasive biomarkers of heart transplant rejection. *Eur Heart J.* 2014; 35\(45\):3194-3202.](#)
- 26-40. Yamani MH, Taylor DO, Haire C, et al. Post-transplant ischemic injury is associated with up-regulated AlloMap gene expression. *Clin Transplant.* 2007a; 21(4):523-525.
- 27-41. Yamani MH, Taylor DO, Rodriguez ER, et al. Transplant vasculopathy is associated with increased AlloMap gene expression score. *J Heart Lung Transplant.* 2007b; 26(4):403-406.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Berry GJ, Burke MM, Andersen C, et al. The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. *J Heart Lung Transplant.* 2013; 32(12):1147-1162.
2. Blue Cross Blue Shield Association. Gene Expression Profiling as a Noninvasive Method to Monitor for Cardiac Allograft Rejection. TEC Assessment, 2011; 26(8).
3. CareDx. Outcomes AlloMap Registry: the Long-term Management and Outcomes of Heart Transplant Recipients With AlloMap Testing (OAR). NLM Identifier: NCT01833195. Last updated Feb. 5, 2020. Available at: <https://clinicaltrials.gov/ct2/show/NCT01833195?term=AlloMap>. Accessed on March 19, 2021~~January 19, 2021~~.
4. [CareDx. Utility of Donor-Derived Cell Free DNA in Association With Gene Expression Profiling \(D-OAR\). NLM Identifier: NCT02178943. Last updated January 30, 2019. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02178943?term=NCT02178943&draw=2&rank=1. Accessed on March 18, 2021.](#)
5. [CareDx. AlloSeq cfDNA, a donor-derived cell-free DNA measurement solution for on-site monitoring of solid organ transplants. Available at: https://caredx.com/wp-content/uploads/2020/10/P198-Poster-AQ-cfDNA-1.pdf. Accessed on March 18, 2021.](#)

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

- 4-6. Centers for Medicare and Medicaid Services. National Coverage determination. Heartsbreath Test for Heart Transplant Rejection. NCD #260.10. December 8, 2008. Available at: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=325&ncdver=1&DocID=260.10&from2=index_chapter_list.asp&list_type=&bc=gAAAAAgAAAAAAA%3d%3d&. Accessed on ~~March 19, 2021~~ January 19, 2021.
7. Colvin MM, Cook JL, Chang P, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: A Scientific Statement from the American Heart Association. *Circ.* 2015; 131(18):1608-1639.
- 5-8. Costanzo MR, Dipchand A, Starling R. et al. The International Society of Heart and Lung Transplantation guidelines for the care of heart transplant recipients. *J Heart Lung Transplant.* 2010; 29(8):914-956. Available at: [http://www.jhltonline.org/article/S1053-2498\(10\)00358-X/abstract](http://www.jhltonline.org/article/S1053-2498(10)00358-X/abstract). Accessed on ~~March 19, 2021~~ January 19, 2021.
- 6-9. Francis GS, Greenberg BH, Hsu DT, et al. ACCF/AHA/ACP/HFSA/ISHLT 2010 clinical competence statement on management of patients with advanced heart failure and cardiac transplant: a report of the ACCF/AHA/ACP Task Force on Clinical Competence and Training. *Circulation.* 2010; 122(6):644-672. Available at: <http://circ.ahajournals.org/content/122/6/644.full.pdf>. Accessed on ~~March 19, 2021~~ January 19, 2021.
10. National Heart, Lung and Blood Institute (NHLBI). *Genome Transplant Dynamics*. NLM Identifier: NCT02423070. Last updated March 12, 2021. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT02423070?term=NCT02423070&draw=2&rank=1>. Accessed on March 18, 2021.
- 7-11. Society for Cardiovascular Pathology. International Society for Heart and Lung Transplantation (ISHLT) revised grading criteria. 2014.
- 8-12. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant.* 2005; 24(11):1710-1720.
- 9-13. Taylor D, Meiser B, Webber, S, et al. The International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the Care of Heart Transplant Recipients, Task Force 2: Immunosuppression and Rejection. 2010 Nov. 8; 1-41.
- 10-14. Tice JA. California Technology Assessment Forum (CTAF). Gene expression profiling for the diagnosis of heart transplant rejection. A Technology Assessment. San Francisco, CA: CTAF; October 13, 2010.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

- ~~11-15.~~ U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). New Humanitarian Device Approval. Heartsbreath No. H030004. Rockville, MD:FDA. February 24, 2004. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf3/h030004c.pdf. Accessed on ~~March 19, 2021~~January 19, 2021.
- ~~12-16.~~ U. S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). 510(k) Substantial Equivalence Determination Decision Summary for AlloMap® Molecular Expression Testing. No. K073482. Rockville, MD:FDA. Nov. 4, 2008. Available at: https://www.accessdata.fda.gov/cdrh_docs/reviews/k073482.pdf. Accessed on ~~March 19, 2021~~January 19, 2021.
- ~~13-17.~~ U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Humanitarian Use Device Exemptions. Available at: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm>. Accessed on ~~March 19, 2021~~January 19, 2021.
- ~~14-18.~~ XDx, Inc. A Comparison of AlloMap Molecular Testing and Traditional Biopsy-based Surveillance for Heart Transplant Rejection Early Post-transplantation (EIMAGE). NLM Identifier: NCT00962377. Last updated December 21, 2010. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00962377?term=AlloMap&rank=1>. Accessed on ~~March 19, 2021~~January 19, 2021.
- ~~15-19.~~ XDx, Inc. Cardiac Allograft Rejection Gene Expression Observational (CARGO) II STUDY (CARGOII). NLM Identifier: NCT00761787. Last updated March 9, 2009. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00761787?term=AlloMap&rank=2>. Accessed on ~~March 19, 2021~~January 19, 2021.
- ~~16-20.~~ XDx, Inc. IMAGE: A Comparison of AlloMap Molecular Testing and Traditional Biopsy-based Surveillance for Heart Transplant Rejection. NLM Identifier: NCT00351559. Last updated November 20, 2009. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00351559?term=00351559&rank=1>. Accessed on ~~March 19, 2021~~January 19, 2021.

Index

- AlloMap
- [AlloSure Heart](#)
- [AlloSeq cfDNA](#)

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

[MMDx](#)

[myTAI_{HEART}](#)

Breath Test as an Aid for Diagnosis of Heart Transplant Rejection

[Donor-derived cell free DNA, dd-cfDNA](#)

Gene Expression Molecular Profiling

Heartsbreath

[Presage ST₂](#)

[Viracor TRAC Heart dd-cfDNA](#)

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	05/13/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. A statement was added for other noninvasive tests considered INV and NMN. The Rationale, Background, Definitions, References and Index were updated. Updated Coding section; added 0055U, 0087U, 0118U and 81479, 81599 NOC.
Reviewed	02/11/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. References were updated.
	12/16/2020	Updated Coding section with 01/01/2021 CPT changes; added 84999 replacing 0085T deleted 12/31/2020.
Reviewed	02/20/2020	MPTAC review. References were updated.
Reviewed	03/21/2019	MPTAC review. References were updated.
Reviewed	05/03/2018	MPTAC review. The document header wording was updated from “Current Effective Date” to “Publish Date.” References were updated.
Reviewed	05/04/2017	MPTAC review. The Rationale and References sections were updated.
Reviewed	05/05/2016	MPTAC review. References were updated.
	01/01/2016	Updated Coding section with 01/01/2016 CPT changes; removed ICD-9 codes.
Reviewed	05/07/2015	MPTAC review. References were updated.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

[This Medical Policy provides assistance in understanding Healthy Blue’s standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue’s Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.](#)

Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection

Reviewed	05/15/2014	MPTAC review. The Rationale and References were updated.
Reviewed	05/09/2013	MPTAC review. References were updated.
Reviewed	05/10/2012	MPTAC review. The Background and References were updated.
Revised	05/19/2011	MPTAC review. The position on AlloMap molecular expression testing has been changed to now consider medically necessary when criteria are met. The Rationale, Background, Coding and Reference sections were updated.
Reviewed	05/13/2010	MPTAC review. The Background and Reference sections were updated.
Reviewed	05/21/2009	MPTAC review. Updated Reference section.
Reviewed	05/15/2008	MPTAC review. References were updated.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review. Reference section was updated.
Reviewed	06/08/2006	MPTAC review. References were updated and information was added about the CARGO Study of AlloMap testing.
Revised	07/14/2005	MPTAC review. AlloMap [®] molecular testing added as investigational/not medically necessary.
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations

	Last Review Date	Document Number	Title
Anthem, Inc.			No prior document
WellPoint Health Networks, Inc.	12/02/2004	2.04.32	Breath Test for Use as an Aid in the Diagnosis of Heart Transplant Rejection

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.