



Louisiana

Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148

Original Effective Date: 01/31/2005

Current Effective Date: 12/01/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider AlloMap^{TM†} molecular expression testing as a non-invasive method of determining the risk of rejection in heart transplant recipients to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for AlloMap molecular expression testing will be considered when all of the following criteria are met:

- Patient is at least 15 years of age; and
- Between 6 months and 5 years post-transplant; and
- Recipient must have stable heart allograft function (i.e., left ventricular ejection fraction 45% or greater, no evidence of congestive heart failure); and
- Testing is performed in lieu of routinely scheduled endomyocardial biopsies and result will be used to determine the need for subsequent endomyocardial biopsy to clarify rejection status.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers the measurement of volatile organic compounds with the Heartsbreath™‡ test to assist in the detection of grade 2R (formerly grade 3) heart transplant rejection to be **investigational**.*

Based on review of available data, the Company considers the use of peripheral blood measurement of donor-derived cell-free DNA testing for transplant rejection status **investigational***, including but not limited to the following:

- The AlloSure test in the management of patients after renal transplantation, including but not limited to the detection of acute renal transplant rejection or renal transplant graft dysfunction;
- The myTAIHEART assay in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection.

Based on review of available data, the Company considers other tests and uses of AlloMap™‡ molecular expression testing when the above criteria are not met to be **investigational**.*

Policy Guidelines

The U.S. Food and Drug Administration has indicated that the Heartsbreath (Menssana Research) test is only for use as an aid in the diagnosis of grade 3 (now known as grade 2R) heart transplant rejection in patients who have received heart transplants within the preceding year and who have had endomyocardial biopsy within the previous month.

Background/Overview

Heart Transplant Rejection

Noninvasive Heart Transplant Rejection Tests

The Heartsbreath test, a noninvasive test that measures breath markers of oxidative stress, has been developed to assist in the detection of heart transplant rejection. In heart transplant recipients, oxidative stress appears to accompany allograft rejection, which degrades membrane polyunsaturated fatty acids and evolving alkanes and methylalkanes that are, in turn, excreted as volatile organic compounds in breath. The Heartsbreath test analyzes the breath methylated alkane contour, which is derived from the abundance of C4 to C20 alkanes and monomethylalkanes and has been identified as a marker to detect grade 3 (clinically significant) heart transplant rejection.

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Another approach has focused on patterns of gene expression of immunomodulatory cells, as detected in the peripheral blood. For example, microarray technology permits the analysis of the expression of thousands of genes, including those with functions known or unknown. Patterns of gene expression can then be correlated with known clinical conditions, permitting a selection of a finite number of genes to compose a custom multigene test panel, which then can be evaluated using polymerase chain reaction techniques. AlloMap is a commercially available molecular expression test that has been developed to detect acute heart transplant rejection or the development of graft dysfunction. The test involves polymerase chain reaction-expression measurement of a panel of genes derived from peripheral blood cells and applies an algorithm to the results. The proprietary algorithm produces a single score that considers the contribution of each gene in the panel. The score ranges from 0 to 40. The AlloMap website states that a lower score indicates a lower risk of graft rejection; the website does not cite a specific cutoff for a positive test. All AlloMap testing is performed at the CareDx reference laboratory in California.

Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. They include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most have had low accuracy in diagnosing rejection. Preliminary studies have evaluated the association between heart transplant rejection and micro-RNAs or high-sensitivity cardiac troponin in cross-sectional analyses but the clinical use has not been evaluated.

Renal Transplant Rejection

Donor-Derived Cell-Free DNA Testing

cfDNA, released by damaged cells, is normally present in healthy individuals. In patients who have received transplants, dd-cfDNA may be also present. It is proposed that allograft rejection, which is associated with damage to transplanted cells, may result in an increase in dd-cfDNA. AlloSure is a commercially available, next-generation sequencing assay that quantifies the fraction of dd-cfDNA in renal transplant recipients relative to total cfDNA by measuring 266 single nucleotide variants. Separate genotyping of the donor or recipient is not required but patients who receive a kidney transplant from a monozygotic (identical) twin are not eligible for this test. The fraction of dd-cfDNA relative to total cfDNA present in the peripheral blood sample is cited in the report. All AlloSure testing is performed at the CareDx reference laboratory.

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myTAI_{HEART} Biomarker

Using proprietary myTAI_{HEART} software, the myTAI_{HEART} test uses multiplexed, high-fidelity amplification followed by allele-specific qPCR of a panel of 94 highly informative bi-allelic single nucleotide polymorphisms (SNPs) and two controls to quantitatively genotype cell free DNA in the patient's plasma after cardiac transplant, and accurately distinguish "donor specific" cell free DNA originating from the engrafted heart from "self-specific" cell free DNA originating from the recipient's native cells. The ratio of donor specific cell free DNA to total cell free DNA is reported as the donor fraction (%) and categorizes the patient as at low or increased risk of moderate (grade 2R) to severe (grade 3R) acute cellular rejection: low donor fractions indicate less damage to the transplanted heart and a lower risk for rejection, while increased donor fractions indicate more damage to the transplanted heart and an increased risk for rejection. Testing with myTAI_{HEART} does not require a donor specimen. The test is indicated for use in heart transplant recipients who are 2 months of age or older and ≥ 8 days post-transplant, restricted to use in single organ post-heart transplant patients, and is contraindicated in patients who:

- Are pregnant
- Currently have or in the past have had another transplanted organ (solid organ or allogeneic bone marrow)
- Have post-transplant lymphoproliferative disease
- Have cancer or have had cancer within the previous 2 years
- Are on mechanical circulatory support
- Are closely related to the transplant donor

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2004, the Heartsbreath test (Menssana Research) was cleared for marketing by the U.S. FDA through a humanitarian device exemption for use as an aid in diagnosing grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The device is intended as an adjunct to, and not as a substitute for, endomyocardial biopsy and is also limited to patients who have had endomyocardial biopsy within the previous month.

In 2008, AlloMap Molecular Expression Testing (CareDx, formerly XDx) was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices, in conjunction with clinical assessment, for aiding in the identification

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of heart transplant recipients with stable allograft function and a low probability of moderate-to-severe transplant rejection. It is intended for patients at least 15 years old who are at least 2 months post transplant.

myTAI_{HEART} is a laboratory developed test (LDT) developed for clinical diagnostic performance exclusively in the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendment (CLIA) accredited TAI Diagnostics Clinical Reference Laboratory. This test was developed and its performance characteristics determined by TAI Diagnostics, and has not been cleared or approved by the U.S. FDA.

Rationale/Source

Several commercially available laboratory tests assess heart transplant rejection, including the Heartsbreath test, which measures breath markers of oxidative stress, and the AlloMap test, which uses gene expression profiling. These tests create a score based on the expression of a variety of immunomodulatory genes and are proposed as an alternative or as an adjunct to invasive endomyocardial biopsy. Renal transplant rejection may be assessed by the AlloSure test, which measures the donor-derived cell-free DNA in peripheral blood and is proposed as an alternative or as an adjunct to invasive renal biopsy.

For individuals who have a heart transplant who receive a measurement of volatile organic compounds to assess cardiac allograft rejection, the evidence includes a diagnostic accuracy study. The relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The published study found that, for identifying grade 3 (now grade 2R) rejection, the negative predictive value of the breath test the study evaluated (97.2%) was similar to endomyocardial biopsy (96.7%) and the sensitivity of the breath test (78.6%) was better than that for biopsy (42.4%). However, the breath test had a lower specificity (62.4%) and a lower positive predictive value (5.6%) in assessing grade 3 rejection than a biopsy (specificity, 97%; positive predictive value, 45.2%). The breath test was also not evaluated for grade 4 rejection. This single study is not sufficient to determine the clinical validity of the test measuring volatile organic compounds and no studies on clinical utility were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

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For individuals who have a heart transplant who receive gene expression profiling (GEP) to assess cardiac allograft rejection, the evidence includes two diagnostic accuracy studies and several randomized controlled trials evaluating clinical utility. The relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The 2 studies, Cardiac Allograft Rejection Gene Expression Observation (CARGO, CARGO II) examining the diagnostic performance of GEP for detecting moderate-to-severe rejection lacked a consistent threshold for defining a positive GEP test (ie, 20, 30, or 34) and reported a low number of positive cases. In the available studies, although the negative predictive values were relatively high (ie, at least 88%), the performance characteristics were only calculated based on 10 or fewer cases of rejection; therefore, performance data may be imprecise. Moreover, the positive predictive value in CARGO II was only 4.0% for patients who were at least two to six months post transplant and 4.3% for patients more than six months post transplant. The threshold indicating a positive test that seems to be currently accepted (a score of 34) was not prespecified; rather it evolved partway through the data collection period in the Invasive Monitoring Attenuation through Gene Expression (IMAGE) study. In addition, the IMAGE study had several methodologic limitations (eg, lack of blinding); further, the IMAGE study failed to provide evidence that GEP offers incremental benefit over biopsy performed on the basis of clinical exam or echocardiography. Patients at the highest risk of transplant rejection are patients within one year of the transplant, and, for that subset, there remains insufficient data on which to evaluate the clinical utility of GEP. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a renal transplant and clinical suspicion of allograft rejection who receive testing of donor-derived cell-free DNA to assess renal allograft rejection, the evidence includes a diagnostic accuracy study. The relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The study examined the diagnostic performance of donor-derived cell-free DNA for detecting moderate-to-severe rejection; the negative predictive value was moderately high (84%), and performance characteristics were calculated on 27 cases of active transplant rejection. The threshold indicating a positive test was not prespecified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heart transplantation who receive myTAI_{HEART} assay to determine acute cellular rejection, the evidence includes observational studies. A validation study using 158 matched endomyocardial biopsy-plasma pairs from 76 pediatric and adult heart transplant recipients (ages 2 months or older, and 8 days more post-transplant) found a donor-specific fraction cutoff (0.32%)

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that produced a 100% negative predictive value for Grade 2 or higher acute cellular rejection. A prospective observational blinded study (n=174; pediatric=101, adult=73) using biopsy-paired samples found that myTAI_{HEART} level was associated with acute cellular and antibody-mediated rejection in both adult and pediatric heart transplant populations, and that an optimal donor fraction threshold (0.3%) ruled out the presence of either acute cellular rejection or antibody-mediated rejection. Both studies received industry funding. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received from 7 academic medical centers and 1 specialty society while this policy was under review in 2012. Input was mixed on whether AlloMap should be investigational. Four reviewers agreed with the investigational status, one disagreed, and three indicated it was a split decision/other. Reviewers generally agreed that the sensitivity and specificity have not yet been adequately defined for AlloMap and that the negative predictive value was not sufficiently high to preclude the need for biopsy. There was mixed input about the need for surveillance cardiac biopsies to be performed in the absence of clinical signs and/or symptoms of rejection.

2008 Input

In response to requests, input was received from 2 academic medical centers and 2 physician specialty societies while this policy was under review in 2008. Three reviewers agreed that these approaches for monitoring heart transplant rejection are considered investigational. The American College of Cardiology disagreed with the policy, stating that the College considers the available laboratory tests to have good potential to diagnose heart transplant rejection and reduce the frequency of invasive biopsies performed on heart transplant patients, although questions remained as to their role in clinical practice.

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Practice Guidelines and Position Statements

International Society of Heart and Lung Transplantation

The International Society of Heart and Lung Transplantation (2010) issued guidelines for the care of heart transplant recipients. The guidelines included the following recommendations (see Table 1).

Table 1. Guidelines for Postoperative Care of Heart Transplant Recipients

Recommendation	COR	LOE
“The standard of care for adult HT recipients is to perform periodic EMB during the first 6 to 12 postoperative months for surveillance of HT rejection.”	IIa	C
“After the first post-operative year, EMB surveillance for an extended period of time (eg, every 4-6 months) is recommended in HT patients at higher risk for late acute rejection....”	IIa	C
“Gene Expression Profiling (AlloMap) 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 after HT.”	IIa	B

ACR: acute heart rejection; COR: class of recommendation; EMB: endomyocardial biopsy; HT: heart transplant; LOE: level of evidence.

Kidney Disease Improving Global Outcomes

The Kidney Disease Improving Global Outcomes (2009) issued guidelines for the care of kidney transplant recipients. The guidelines included the following recommendations (see Table 2).

Table 2. Guidelines for Biopsy in Renal Transplant Recipients

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Recommendation	SOR	LOE
“We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine.”	Level 1	C
“We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection.”	Level 2	D
“We suggest kidney allograft biopsy every 7-10 days during delayed function.”	Level 2	C
“We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1-2 months after transplantation.”	Level 2	D
“We suggest kidney allograft biopsy when there is new onset of proteinuria.”	Level 2	C
“We suggest kidney allograft biopsy when there is unexplained proteinuria ≥ 3.0 g/g creatinine or ≥ 3.0 g per 24 hours.”	Level 2	C

LOE: level of evidence; SOR: strength of recommendation.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2008) issued a noncoverage decision for the Heartsbreath test. The Centers determined that the evidence did not adequately define the technical characteristics of the test; nor did it demonstrate that Heartsbreath testing could predict heart

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transplant rejection, and therefore the test would not improve health outcomes in Medicare beneficiaries.

For AlloMap, there is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers. Palmetto (2012) conducted a technical assessment and determined that AlloMap met Medicare’s reasonable and necessary criteria.

For AlloSure, there is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers. Palmetto GBA and Noridian have local coverage determinations on AlloSure.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Active Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT01833195 ^a	Outcomes AlloMap Registry: the Long-term Management and Outcomes of Heart Transplant Recipients With AlloMap Testing (OAR)	2000	Feb 2020
NCT02178943 ^a	Utility of Donor-Derived Cell-free DNA in Association With Gene-	100	Feb 2020

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	Expression Profiling (AlloMap [®])‡ in Heart Transplant Recipients (D-OAR)		
NCT03326076 ^a	Evaluation of Patient Outcomes From the Kidney Allograft Outcomes AlloSure Registry	1000	Dec 2022

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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- 12/07/2004 Medical Director review
- 12/14/2004 Medical Policy Committee review
- 01/31/2005 Managed Care Advisory Council approval
- 07/07/2006 Format revision, including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
- 01/10/2007 Medical Director review
- 01/17/2007 Medical Policy Committee approval. New policy statement added regarding evaluation of genetic expression in the peripheral blood.
- 01/07/2009 Medical Director review
- 01/14/2009 Medical Policy Committee approval. No change to coverage.
- 01/07/2010 Medical Policy Committee approval
- 01/20/2010 Medical Policy Committee Implementation approval. No change to coverage.
- 01/06/2011 Medical Policy Committee approval
- 01/19/2011 Medical Policy Committee Implementation approval. No change to coverage.
- 03/01/2012 Medical Policy Committee review
- 03/21/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 05/02/2013 Medical Policy Committee review

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05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Added “ Based on review of available data, the Company considers AlloMap molecular expression testing as a non-invasive method of determining the risk of rejection in heart transplant recipients to be eligible for coverage.” Used to be considered investigational.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Added grade 2R category to policy statement.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Policy statement added that “The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation, including but not limited to the detection of acute renal transplant rejection or renal transplant graft dysfunction, is considered investigational.” Title expanded to include kidney transplant rejection.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. No change to coverage.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Added criteria for AlloMap. Added the myTAIHEART assay as investigational.
12/11/2020	Coding update

Next Scheduled Review Date: 09/2021

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Louisiana

Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148

Original Effective Date: 01/31/2005

Current Effective Date: 12/01/2020

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0055U, 0087U, 0088U, 0118U, 81479, 81595, 86849 Code deleted eff 1/1/2021: 0085T
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

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standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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