Introduction

AlloSure for kidney transplant rejection is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
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<tbody>
<tr>
<td>AlloSure</td>
<td>81479</td>
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</table>

What Is Kidney Transplant Rejection

Definition

Kidney disease is a loss of renal function which, without treatment, leads to eventual build-up of waste and other toxic substances in the blood. Treatment of advanced kidney disease, called end-stage kidney disease, consists of dialysis or renal transplant. Transplant rejection can be acute or chronic.

Incidence and Prevalence

According to the National Kidney Foundation, 97% of kidney transplants are functioning 1 month after transplant, and 80% are functioning after 3 years. Approximately 20% of kidney transplants performed each year are repeat transplants.

Symptoms

Kidney transplant rejection can be acute (occurring suddenly and progressing quickly) or chronic (occurring slowly over time), and is typically immune system mediated. Symptoms of transplant rejection include fever and flu-like symptoms, decreased urinary output, weight gain, fatigue, and pain over the transplanted organ.

Acute rejection of the donated kidney is thought to lead to tissue injury, including increased cell death in the allograft, which then leads to increased donor-derived cell free DNA (dd-cfDNA) in the bloodstream.
Cause

Transplanted kidneys can fail for multiple reasons:2

- Blood clot in the vessels leading to the kidney
- Infection
- Medication side effects
- Non-compliance with post-transplant medications and other post-surgical care
- Recurrence of the original medical problem that caused the kidney transplant
- Acute or chronic rejection caused by immune-mediated donor kidney damage

Diagnosis

Rise in creatinine levels is currently used to initially diagnose graft rejection, and the gold standard for initial diagnosis is histological analysis based on needle biopsy of the organ.4-5 However, organ biopsy is invasive and often associated with complications, patient discomfort, and inconvenience. Serum creatinine is one of the main markers used to monitor allograft functioning, but has been shown to lack sensitivity and specificity for graft injury.4-5

Alternatively, donor-derived cell-free DNA (dd-cfDNA) (as a fraction of the total cell-free DNA [cfDNA]) has been proposed as a noninvasive marker for detecting graft rejection and measuring allograft damage among recent kidney transplant patients.

Treatment

Renal transplantation has been shown to increase the survival and quality of life (QOL) of patients with end stage renal disease (ESRD), and is often considered the preferred treatment option for these patients.6 When a transplanted kidney is rejected, dialysis is performed until another organ can be procured for transplant.

Survival

If the kidneys fail completely, survival is a few months without treatment.1 After transplant, long-term survival is still limited, and acute rejection is a frequent complication and associated with reduced graft survival.1

Test Information

Introduction

AlloSure is an assay designed to detect allograft rejection in kidney transplant recipients.
Description and Purpose

According to the manufacturer of AlloSure (Care Dx, Inc), the test is intended to non-invasively measure donor DNA in the blood for kidney transplant surveillance of active donor graft rejection.\(^7\) Active rejection as defined by the manufacturer includes “T cell–mediated rejection [TCMR], “acute/active” antibody-mediated rejection [ABMR], and “chronic, active” ABMR”).\(^7\) The test is intended for patients 18 years of age or older who are at least 2 weeks post-transplant.

Test Targets

AlloSure is a targeted next-generation sequencing assay that uses 266 single-nucleotide polymorphisms (SNPs) to quantify dd-cfDNA in transplant patients.\(^7\)

Result

The test reports the percent of donor derived DNA in the patient’s blood sample along with quality control cut-off values.\(^7\)

Interpretation of test results:\(^8\)

- “Greater than 1% dd-cfDNA is associated with active rejection.”
- “0.21% dd-cfDNA is the median observed in a reference population of stable recipients.”
- “Greater than 61% increase in dd-cfDNA from a prior sample exceeds the biological and analytical variability observed in the reference population.”

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to AlloSure for Kidney Transplant Rejection.

The Transplantation Society

The Transplantation Society, via the Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group, states the following regarding acute rejection, renal allograft function, and renal allograft biopsy:\(^9\)

Treatment of Acute Rejection

- “6.1: We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. (1C)”
- “6.2: We suggest treating subclinical and borderline acute rejection. (2D)”
• “6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. (1D)”
• “6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. (2D)”
• “6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. (2C)”
• “6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C)”
  o “plasma exchange”
  o “intravenous immunoglobulin”
  o “anti-CD20 antibody”
  o “lymphocyte-depleting antibody”
• “6.5: For patients who have a rejection episode, we suggest adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. (2D)”

Kidney Allograft Biopsy

• “9.1: We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (1C)”
• “9.2: We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D)”
• “9.3: We suggest kidney allograft biopsy every 7–10 days during delayed function. (2C)”
• “9.4: We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1–2 months after transplantation. (2D)”
• “9.5: We suggest kidney allograft biopsy when there is”
  o “new onset of proteinuria (2C)”
  o “unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 proteinuria >3.0g/g creatinine or >3.0g per 24 hours. (2C)”

The Renal Association

The Renal Association clinical practice guideline for renal transplant post-operative care states the following regarding transplant rejection:\textsuperscript{10}

• “Guideline 4.1 – KTR: diagnosis of acute rejection”
“We recommend that a transplant renal biopsy should be carried out before treating an acute rejection episode unless this will substantially delay treatment or pose a significant risk to the patient (1C)”

• “Guideline 5.2 – KTR: detection of chronic allograft injury”
  “We suggest that renal function should be monitored at each clinic visit by assessment of serum creatinine and qualitative evaluation of urine protein excretion by dipstick, supplemented by spot protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR) if positive (2C)”

• “Guideline 5.3 – KTR: diagnosis of chronic allograft injury”
  “We suggest that renal biopsy is the optimal investigation for parenchymal causes of graft dysfunction where the cause is uncertain (2C)”

Literature Review

There is a limited evidence base for the validity of AlloSure which includes one analytical validity study and one clinical validity study, both of moderate quality. These studies are hampered by small numbers of affected individuals. In addition, the studies were non-blinded, possibly introducing assessment bias.

Additional well-designed studies are needed to establish the clinical validity and clinical utility of the AlloSure test, including assessment of AlloSure’s impact on clinically relevant health outcome measures, including morbidity and mortality. Additional research is needed to clarify the need for ongoing surveillance of dd-cfDNA post-transplant and how clinicians should approach cases in which the clinical presentation and dd-cfDNA results are in disagreement.

Ongoing Clinical Trial

• NCT Number: NCT03326076
• Title: Evaluation of Patient Outcomes From the Kidney Allograft Outcomes AlloSure Registry

Criteria

Introduction

Requests for AlloSure testing for allograft kidney transplant rejection are reviewed using the following criteria.

This test is considered investigational and/or experimental.

• Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is
insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References

Introduction

This guideline cites the following references.


7. CareDX. Available at: http://www.allosure.com/.


