Test Specific Guidelines

AlloSure for Kidney Transplant Rejection

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Introduction

AlloSure for kidney transplant rejection is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure code
AlloSure	81479

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.[1] 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.[2] Approximately 20% of kidney transplants performed each year are repeat transplants.[2]

Symptoms

Kidney transplant rejection can be acute (occurring suddenly and progressing quickly) or chronic (occurring slowly over time), and is typically immune system mediated.[2] Symptoms of transplant rejection include fever and flu-like symptoms, decreased urinary output, weight gain, fatigue, and pain over the transplanted organ.[3]

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. Other investigators have reported

that the fraction of cell-free DNA (cfDNA) originating from the organ grafts is approximately less than 1% and during rejection, level of dd-cfDNA increase.[4-6]

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. Biopsy is also prone to sampling error. 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 and may change too late to allow prompt clinical management decisions.[7,8]

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.[9] 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.[10] Active rejection as defined by the manufacturer includes "T cell–mediated rejection [TCMR], "acute/active" antibody-mediated rejection [ABMR], and "chronic, active" ABMR)".[10] 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.[10]

Result

The test reports the percent of donor derived DNA in the patient's blood sample along with quality control cut-off values.[10]

Interpretation of test results:[11]

- **Low rejection risk: <0.5%**
- **Graft injury onset: 0.5-1.0%**
- **High rejection risk: 1.0-2.9%**

In addition, the relative change of dd-cfDNA over time can provide additional information:[11]

- **"Increases in AlloSure results over 61% exceed biological variation"**
- **"A median increase of 149% between serial results is indicative of graft injury"**

Guidelines and Evidence

Introduction

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

The Renal Association

The Renal Association (RA, 2017) clinical practice guideline for renal transplant post-operative care states the following regarding transplant rejection:[12]

- **"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)**

The Transplantation Society

The Transplantation Society, via the Kidney Disease: Improving Global Outcomes (KDIGO, 2009) Transplant Work Group, states the following regarding acute rejection, renal allograft function, and renal allograft biopsy:[13]

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)"**
- **"6.3.1: 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)"**
  - **"plasma exchange"**
  - **"intravenous immunoglobulin"**
  - **"anti-CD20 antibody"**
  - **"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"
    - "new onset proteinuria (2C)"
    - "unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 proteinuria >3.0g/g creatinine or >3.0g per 24 hours. (2C)"

Selected Relevant Publications

The studies are of moderate quality and provide a limited evidence base for the validity of AlloSure as an independent and replacement test for detecting graft rejection and measuring allograft damage among recent kidney transplant patients.[14-21] These studies are hampered by small sample size, competing co-morbidities, variable timing of samples, and/or non-blinded or retrospective study design.

Additional well-designed studies are needed to establish the clinical validity and 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.

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

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