



Monitoring the Health of Transplanted Organs

A large graphic element consisting of a dark blue shape on the left and a white shape on the right, separated by a diagonal line. The white shape contains the "myTAI HEART" logo. The "my" is in a lowercase, blue, cursive font, "TAI" is in a large, blue, bold, sans-serif font, and "HEART" is in a smaller, blue, bold, italicized, sans-serif font below it. The dark blue shape contains the text "DONOR GENOTYPING MANUAL" in white, bold, sans-serif font.

**DONOR
GENOTYPING MANUAL**

*my***TAI**
HEART



TABLE OF CONTENTS

| | | |
|------|---|---|
| I | Intended Use..... | 1 |
| II | Warnings and Limitations..... | 1 |
| III | Introduction..... | 1 |
| IV | Summary and Explanation of the myTAI _{HEART} Test..... | 2 |
| V | Customer Support Contact Information..... | 2 |
| VI | Equipment and Supplies Required by User..... | 3 |
| VII | Supplies Provided by TAI Diagnostics..... | 3 |
| VIII | Disclaimers and Precautions..... | 3 |
| IX | Order Process..... | 3 |
| X | Donor Specimen Collection..... | 4 |
| XI | Recipient Specimen Collection..... | 5 |
| XII | Test Requisition Form and Test Orders..... | 5 |
| XIII | Notice of Specimen Rejection..... | 5 |
| XIV | Specimen Shipping..... | 6 |
| XV | References..... | 7 |

SECTION I: INTENDED USE

myTAI_{HEART} is a laboratory developed test (LDT) performed in a single laboratory, which measures the donor fraction of cell-free DNA in plasma separated from a whole blood sample as a marker for transplanted organ injury. This test is intended to aid in the identification of heart transplant recipients who have a low probability of moderate/severe acute cellular rejection (Grade 2R or higher) at the time of testing in conjunction with standard clinical assessment. This test is indicated for use in heart transplant recipients who are 2 months of age or older and at least 1 week post-transplant (≥7 days).

SECTION II: WARNINGS AND LIMITATIONS

myTAI_{HEART} quantitates the donor fraction of cfDNA in the circulation of heart transplant recipients. This test may provide a false positive or false negative result under certain clinical conditions. Patients treated for rejection within 28 days of sample collection may have variably elevated donor fractions. Clinical judgment will be required for interpretation of results. A heart transplant recipient with a negative result should continue to be monitored according to standard clinical care. All results should be interpreted in the context of the patient's clinical findings, history, and laboratory results. Clinical correlation is advised.

CONTRAINDICATIONS:

myTAI_{HEART} is currently for use in single organ post-transplant patients. This test is not intended for patients who:

- are pregnant
- have another transplanted organ
- have post-transplant lymphoproliferative disease
- currently have cancer, or have had cancer within the previous 2 years
- are on mechanical circulatory support

This test was developed and its performance characteristics determined by TAI Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. This Laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.

SECTION III: INTRODUCTION

Today in the United States, over 180,000 people are living with solid organ transplants. Each year over 2,000 heart transplants, including 300 pediatric heart transplants, are performed resulting in over 20,000 living heart transplant recipients¹. One year survival following heart transplantation has improved to 90%. However, 10 year survival remains less than 60%². The heart rejection rate for the first year is approximately 15% and in the second year is approximately 5%. Rejection following solid organ transplantation is the major determinant of clinical outcome. Early treatment with immunosuppressive therapy improves graft function and survival, and decreases recipient mortality³.

TAI Diagnostics provides non-invasive and highly sensitive diagnostic tests to monitor the health of patients who have received solid organ transplants. myTAI_{HEART} is a non-invasive test that requires only a small blood sample for processing in our accredited clinical reference lab and utilizes patent-pending quantitative genotyping technology to measure graft health in heart transplant patients. The technology precisely quantifies the DNA released by injured heart cells into the bloodstream as a direct measurement of transplant injury. TAI Diagnostics' scientific data indicates that the quantitative genotyping technique has a high degree of sensitivity and specificity, and a rapid turnaround time.

SECTION IV: SUMMARY AND EXPLANATION OF THE myTAI_{HEART} TEST

TEST DESCRIPTION

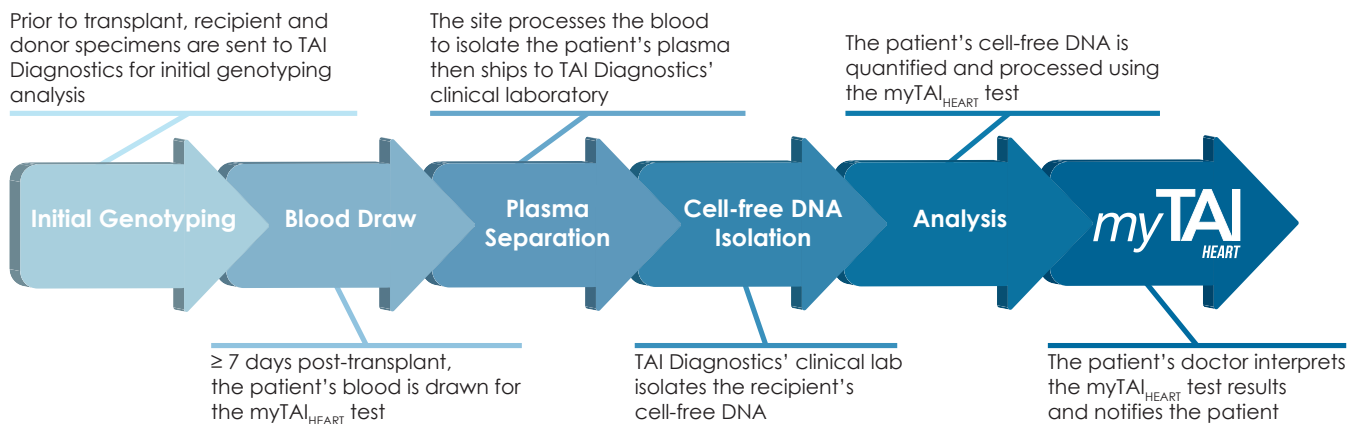
The myTAI_{HEART} test uses a panel of highly informative single nucleotide polymorphisms to quantitatively genotype cell-free DNA (cfDNA) in the patient's plasma. This measurement accurately distinguishes "donor specific" cfDNA originating in the engrafted heart from "self specific" cfDNA originating in the recipient's native cells. The myTAI_{HEART} test reports the ratio of donor specific cfDNA to total cfDNA as the donor fraction (%) and categorizes the patient as at low or increased risk of rejection. Results and additional data are provided to the ordering clinician on the TAI Diagnostics – myTAI_{HEART} Results Report.

TESTING PROCESS

The testing process for the myTAI_{HEART} is diagrammed in the figure below. Prior to ordering the myTAI_{HEART} test for the first time, initial genotyping analysis must be performed on both the patient (heart transplant recipient) as well as the donor specimen. Instructions on obtaining and shipping a recipient / patient specimen for initial genotyping analysis can be found on our website (www.taidiagnostics.com) or by contacting our Customer Support Department (1-888-214-3151). Donor Genotyping kits are supplied free of charge and can be ordered online or by contacting TAI Diagnostics directly. After initial recipient and donor genotyping has been completed, subsequent patient testing will not require a donor sample.

At TAI Diagnostics, the patient's cell-free DNA is isolated, then quantified and processed using the myTAI_{HEART} test. The results are reported to the ordering physician on the next business day (upon receipt at TAI Diagnostics' clinical lab). The physician then interprets the results and determines the course of action for the patient. More details can be found in Section XII: *Test Requisition Form (TRF) and Test Orders*.

Figure 1: Overview of the myTAI_{HEART} Testing Process



SECTION V: CUSTOMER SUPPORT CONTACT INFORMATION

TAI DIAGNOSTICS CUSTOMER SUPPORT

Telephone 1-888-214-3151
 Fax 1-888-300-9674
 Email customersupport@taidiagnostics.com

ORDERING KITS

myTAI_{HEART} Donor Genotyping kits with prepaid return shipping are available for U.S. clients. To order kits, submit requests through our electronic order form (see website) or contact our customer support department at the telephone number and email address listed below.

Telephone 1-888-214-3151
 Email customersupport@taidiagnostics.com

Business Hours: 8 AM to 5 PM Monday through Friday (Central Standard Time). Contact TAI Diagnostics if shipping samples outside of normal business hours.

SECTION VI: EQUIPMENT AND SUPPLIES REQUIRED BY USER

- Hospital / Laboratory label containing a minimum of patient name and date of birth (only needed if sending in a recipient sample for initial genotyping analysis at the same time as the donor sample)
- Parafilm
- Freezer (-20°C or colder)
- Approximately 7 pounds of dry ice per shipment (if sending donor tissue)
- Packaging tape

SECTION VII: SUPPLIES PROVIDED BY TAI DIAGNOSTICS

| QUANTITY | ITEM |
|-----------------|--|
| 1 | Kit Contents Card |
| 1 | Insulated Styrofoam shipper with transport box |
| 1 | Clear plastic bag |
| 1 | Foam tube holder |
| 1 | Specimen biohazard bag |
| 2 | Lavender top, EDTA blood collection tubes (2.0 ml) |
| 1 | Cryogenic vial (3.0 ml) |
| 2 | Donor specimen labels |
| 1 | myTAI _{HEART} Test Requisition Form |
| 1 | myTAI _{HEART} Donor Genotyping Manual |
| 1 | Return overnight shipping label |
| 1 | Dry ice shipping label |

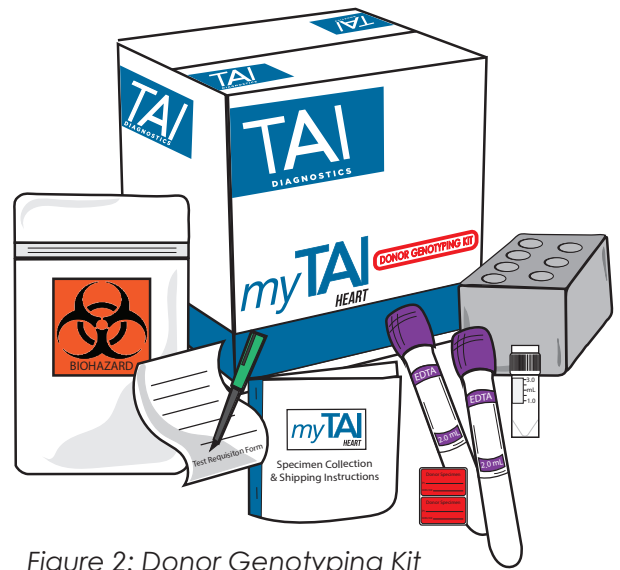


Figure 2: Donor Genotyping Kit

STORAGE CONSIDERATIONS

All items provided by TAI Diagnostics in the myTAI_{HEART} Donor Genotyping kit can be stored at room temperature (18 to 25°C). Do not use kits past their indicated expiration date.

SECTION VIII: DISCLAIMERS AND PRECAUTIONS

- This test is for use with whole blood specimens.
- Avoid contamination of specimens and materials used in the myTAI_{HEART} test.
- Take care not to cross-contaminate samples.
- Do not use kits past their expiration date.
- All disposable items are one time use only. Do not reuse.
- When drawing patient blood, follow your laboratory's universal precautions for blood borne pathogens.
- The provided specimen tubes are unique to the test and should not be switched with other laboratory supplies.
- Wear appropriate personal protective equipment as specified in your laboratory's safety policy.

SECTION IX: ORDER PROCESS

Additional myTAI_{HEART} Test Requisition Forms (TRFs) can be requested via our website (www.taidiagnostics.com) or by contacting our Customer Support Department. To request pre-printed forms with your laboratory information, please submit a request to our customer support team at customersupport@taidiagnostics.com.

Labeling Tubes: Always affix a hospital / laboratory label that includes at least two patient identifiers to each tube used from the collection kit. Use only the tubes provided by TAI Diagnostics in the collection kit

Time of Donor Explant

At the time of donor explant, donor whole blood (2.0 ml EDTA tube) or donor cardiac or lymph node tissue (3.0 ml cryogenic vial) is placed into the appropriate tube from the myTAI_{HEART} Donor Genotyping kit and affixed with a red "Donor Specimen" label.

If a patient (transplant recipient) blood specimen was not previously sent to TAI Diagnostics for initial recipient genotyping analysis, a sample will need to be drawn prior to implant of the heart into the provided EDTA tube of the myTAI_{HEART} Donor Genotyping Kit. The donor (and recipient) samples are shipped to TAI Diagnostics' clinical laboratory.

If shipping donor tissue, the donor and recipient samples are shipped on dry ice to TAI Diagnostics' clinical laboratory. If shipping donor whole blood, the samples can be shipped in the provided box according to your laboratory's protocol for shipping whole blood specimens. Once these specimens are received by TAI Diagnostics, initial genotyping is performed and the results will be utilized for all subsequent post-transplant myTAI_{HEART} testing (donor fraction analysis).

NOTE: Receipt of the donor (and recipient) samples prior to ordering the myTAI_{HEART} Test ensures a rapid turnaround time. Please contact our Customer Support Department for options regarding obtaining a donor specimen after transplant. The donor sample is only required the first time this test is ordered and not needed for subsequent myTAI_{HEART} testing. More details on myTAI_{HEART} specimen requirements and turnaround time can be found on our website or requested through our Customer Support Department.

SECTION X: DONOR SPECIMEN COLLECTION

ITEMS NEEDED FOR COLLECTION OF THE DONOR SPECIMEN

- 2.0 ml lavender top, EDTA whole blood collection tube or 3.0 ml cryogenic vial for tissue
 - Red Donor Specimen Label
 - Parafilm
 - myTAI_{HEART} Test Requisition Form
1. Retrieve the myTAI_{HEART} Donor Genotyping kit from the appropriate storage location in your facility. Most often, this is your central laboratory processing department. Remove a donor specimen tube, red donor specimen label and the test requisition from the myTAI_{HEART} Donor Genotyping Kit.
 - a. For donor whole blood specimen: Use the 2.0 ml lavender top, EDTA tube.
 - b. For donor tissue specimen: Use the 3.0 ml cryogenic vial.
 2. On the red donor specimen label, write the transplant patient's name and MRN/ID# in the spaces provided. This label links the transplant patient (recipient) to the donor specimen. Place the label on the tube that will be used for the donor specimen.
 - a. For a **donor whole blood specimen**: Collect 0.5 to 2.0 ml of donor blood in one of the provided EDTA tubes (now labeled with the red "Donor Specimen" label). Ensure that the cap of the blood tube is screwed on tightly and cover the top with Parafilm. Place the specimen tube in the provided foam rack.
 - b. For a **donor tissue specimen**: Prior to transplant, place a small piece of tissue (cardiac or lymph node) into the provided conical tube (labeled "Donor Specimen"). Ensure that the cryogenic vial cap is screwed on tightly and cover the top of the specimen tube with Parafilm. Place the specimen tube in the provided foam rack and flash freeze according to your laboratory protocol. Alternative tissue specimens are accepted upon approval of TAI Diagnostics' Medical Director.
 3. Confirm the date and time of donor specimen collection in the provided space of the myTAI_{HEART} Test Requisition Form.
 4. If the recipient sample was not sent for initial genotyping prior to transplant and is also being collected at this time, continue to Section XI: Recipient Specimen Collection.

If recipient genotyping wasn't previously performed on the patient at TAI Diagnostics, a patient blood sample will also need to be sent at the time of transplant.

SECTION XI: RECIPIENT SPECIMEN COLLECTION (If not previously sent to TAI Diagnostics)

ITEMS NEEDED FOR COLLECTION OF THE RECIPIENT SPECIMEN

- Lavender top, EDTA whole blood collection tube
 - Hospital / laboratory label with two patient identifiers
 - Parafilm
 - myTAI_{HEART} Test Requisition Form
1. Collect 0.5 – 2.0 mL of whole blood in the additional lavender top, EDTA tube. This extra tube has been provided in the Donor Genotyping Kit for this purpose.
 2. Place a hospital / laboratory label containing at least two patient identifiers onto the patient's whole blood specimen. Ensure that the cap of the blood tube is screwed on tightly and cover the top with parafilm.
 3. Confirm the date and time of recipient specimen collection in the provided space of the myTAI_{HEART} Test Requisition Form
 4. The recipient blood specimen should be packaged and sent along with the donor specimen in the same shipper.

SECTION XII: TEST REQUISITION FORM AND TEST ORDERS

All sections of the test requisition form must be completed when sending in donor specimens for initial genotyping. Once the form is completed, it is highly recommended to fax a copy to TAI Diagnostics (1-888-300-9674). Ensure accuracy in the following sections:

1. PATIENT INFORMATION:
 - a. Include the patient's height, weight, and initial transplant date.
 - b. Enter ICD-10 / Diagnosis codes.
 - c. Check the "Required" box indicating the patient meets the specific criteria for the test. This needs to be signed and dated by a medical professional.
2. TEST(S) REQUESTED:
 - a. If sending donor specimen only: Select "Donor Genotyping (No report issued)."
 - b. If sending a recipient specimen with the donor specimen: Also select "Recipient Genotyping (No report issued)."
3. SPECIMEN SOURCE:
 - a. For the donor sample, select whole blood or tissue.
 - b. If also sending a recipient specimen, select whole blood under the recipient sample section.
4. DONOR SPECIMEN INFORMATION: Confirm the collection date and time.
5. PATIENT (RECIPIENT) SPECIMEN INFORMATION: If also sending a recipient specimen at this time, confirm the collection date and time (do not fill out plasma spin information for this specimen).
6. PROVIDER / ORDERING PHYSICIAN INFORMATION: These sections should be filled out completely and accurately to ensure that patient reports are delivered in a timely manner.
7. REPORT DELIVERY: Select all methods in which result reports should be delivered for the patient.
8. REQUIRED DOCUMENTATION / SPECIAL INSTRUCTIONS: Be sure to include any required documentation with the test requisition form (This includes NY State Non-Permitted Laboratory Test Request approval letter, Medicare signed ABN form, and any relevant medical records).
9. BILLING: Select the desired method of billing and complete the corresponding section in its entirety. Obtain required signatures.

SECTION XIII: NOTICE OF SPECIMEN REJECTION

SPECIMENS WILL BE SUBJECT TO REJECTION FOR THE FOLLOWING REASONS:

- Incomplete and unsigned test requisition.

- Improperly labeled tubes (missing patient identifiers or donor specimen labels).
- Improper shipment of specimens.
- Inadequate quality or quantity of specimen.

TAI Diagnostics will contact the requesting provider regarding an unacceptable specimen and will discuss the options for proceeding at that time.

SECTION XIV: SPECIMEN SHIPPING

ITEMS REQUIRED FOR SHIPPING DONOR GENOTYPING SPECIMENS TO TAI DIAGNOSTICS

- Donor whole blood or flash frozen tissue in labeled specimen tube
- Recipient whole blood specimen (only required if a patient (transplant recipient) specimen was not previously sent to TAI Diagnostics)
- Foam rack
- Specimen biohazard bag
- Completed test requisition form
- Styrofoam shipping box with outer transport box
- Overnight return shipping labels (If sending tissue, you must use the label designated for dry ice. See Figure 3)
- Dry Ice and provided dry ice shipping label if shipping frozen tissue (approximately 7 lbs.)
- Packaging tape

IMPORTANT SAFETY NOTES REGARDING SHIPPING ON DRY ICE

- When handling dry ice, follow your laboratory's safety procedures.
- Never handle dry ice with your bare hands.
- Use dry ice in a ventilated area.
- Store dry ice in an appropriate dry ice storage bin. Do not use airtight containers as these may provide an explosive hazard.
- Dry ice is a skin and eye irritant.
- Use appropriate personal protective equipment when handling dry ice.
- Once you begin this process, work very quickly. Make sure that the tissue sample being shipped DOES NOT THAW.

SHIPPING TISSUE SPECIMENS ON DRY ICE

1. Prepare the shipper by removing the Styrofoam container and any contents from the transport box.
2. For shipping flash frozen tissue specimens, have dry ice ready and keep the tissue sample in the freezer as long as possible.
3. Verify the donor specimen label is filled out with the patient name and MRN/ID information and that it is affixed to the cryogenic vial. The cap must be securely tightened and wrapped in Parafilm.
4. If sending the recipient whole blood sample with the donor tissue sample, confirm that a hospital label with two patient identifiers is affixed to the outside of the blood collection tube, and that the cap is on tight and wrapped with Parafilm.
5. Place the tubes in the foam rack and place the rack inside of the specimen biohazard bag.
6. Prior to shipping, it is recommended that a copy of the test requisition form be faxed to Customer Support at 1-888-300-9674. Fold the completed test requisition form and place it into the large outer pouch of the specimen biohazard bag. Remove the adhesive liner from the flap of the biohazard bag. Press excess air out of the specimen biohazard bag, fold the flap over and seal tightly.
7. Place the biohazard bag containing the sample into the Styrofoam shipping box in an upright position prior to filling with dry ice. Use one shipping box per patient.
8. Fill the Styrofoam shipper with dry ice as full as possible. The Styrofoam lid should sit tightly on the box. Confirm that there is no gap between the lid and the box. Secure the Styrofoam lid tightly with packaging tape and place it inside of the provided cardboard shipping box.

9. Seal the cardboard shipping box with packaging tape.
10. Affix the dry ice label on an outside panel of the provided box. Confirm the dry ice shipping information is visible on the outer shipping box and indicates the appropriate weight of dry ice (7 lbs)
11. TAI Diagnostics uses UPS Next Day Air Shipping Service. FedEx labels are also available.
 - a. Affix the UPS (or FedEx) shipping label (**for dry ice**) to the top of the myTAI_{HEART} shipping box. Examples of the dry ice shipping labels are shown in Figure 3 below and the dry ice designation is circled in red.

SHIPPING WHOLE BLOOD SPECIMENS ONLY

1. Confirm all samples are labeled. If shipping whole blood specimens only, place the blood tubes in the foam rack and place the rack inside of the specimen biohazard bag.

Prior to shipping, it is recommended that a copy of the test requisition form be faxed to Customer Support at 1-888-300-9674.
2. Fold the completed test requisition form and place it into the large outer pouch of the specimen biohazard bag. Remove the adhesive liner from the flap of the biohazard bag. Press excess air out of the specimen biohazard bag, fold the flap over and seal tightly.
3. Place the sample into the Styrofoam shipping box in an upright position. Secure the Styrofoam lid with packaging tape and place inside of the cardboard shipping box.
4. Seal the cardboard shipping box with packaging tape.
5. TAI Diagnostics uses UPS Next Day Air Shipping Service. FedEx labels are also available upon request.
 - a. Use the shipping label that is **NOT** printed for use with dry ice and affix the shipping label to the top of the myTAI_{HEART} shipping box.

TAI Diagnostics accepts deliveries Monday – Friday. The laboratory is closed on all major holidays. All samples should be shipped to the following address:

TAI Diagnostics
Attn: Clinical Laboratory
10101 Innovation Drive, Suite 600
Wauwatosa, WI 53226

Figure 3: Examples UPS and FedEx Dry Ice Shipping Labels



SECTION XV: REFERENCES

1. OPTN / SRTR Annual Report (http://www.ustransplant.org/annual_reports/current/).
2. ISHLT report 2011. J Heart Lung Transplant 30, 1071-1132 (2011).
3. Kaczmarek, I., et al. Successful management of antibody-mediated cardiac allograft rejection with combined immunoadsorption and anti-CD20 monoclonal antibody treatment: case report and literature review. J Heart Lung Transplant 26, 511-515 (2007).

