MMDx Kidney, Heart & Lung
Personalized Transplant Care Through Precision Medicine

What is the Molecular Microscope® Diagnostic System?

MMDx® Kidney, MMDx® Heart and MMDx® Lung are biopsy-based Laboratory Developed Tests that measure gene expression profiling and provide risk assessment for rejection and injury in transplant organs. These tests, which can be used in conjunction with conventional histopathology, measure mRNA transcript levels in the biopsy sample and apply an algorithm to score¹ the results.

The MMDx Kidney, Heart or Lung tests can help stratify the risk for conditions like T-cell mediated rejection (TCMR), antibody-mediated rejection (ABMR), acute and chronic injury, atrophy fibrosis, and arterial hyalinosis.
MMDx combines gene expression technology with the power of big data to deliver objective and reproducible transplant biopsy assessments.

The MMDx algorithm compares the molecular features of the biopsy to those in an organ-specific reference set. The organ-specific reference sets were developed over the course of a decade and consist of over 1600 kidney samples, 1000 heart samples, 600 transbronchial biopsies (TBB) lung samples, and 300 third airway bifurcation (3BMB) mucosal samples.

The reference sets incorporate data that is representative of the global transplant population from early post-transplant to more than 30 years post-transplant.

**Concordance to Histological Biopsy Diagnosis**

Histopathology scores are the primary tool for diagnosing injury or rejection, but studies show frequent disagreement in histological TCMR diagnosis.

Additionally, the quality of the biopsy samples can sometimes impact histology results, rendering the samples unreadable. The MMDx tests for Kidney, Heart and Lung are not intended to replace histology. Rather, they can be used in addition to a histopathologist’s assessment, especially for the objective evaluation of challenging cases.

**Variability in TCMR Diagnosis with Histopathology**

When assessing the same heart biopsy sample, only 28% of pathologists agreed on the diagnosis of TCMR². Likewise, a mere 18% agreed on a TCMR diagnosis for a single lung sample³ and 50% were in agreement after reviewing the same kidney sample¹.
Advantages of MMDx vs. Histology

The MMDx Kidney, Heart and Lung tests complement conventional biopsy and improve the assessment of rejection and injury in transplanted organs.

**Actionable data:** Provides objective and probabilistic risk assessment

**Fast turnaround:** Results available up to 1-2 business days after receipt of the sample

**Easily Incorporated:** Sample is taken from the existing biopsy (requires only 3 mm for kidney, 1-2 bites for heart and lung)

**Efficient Process:** Place biopsied tissue into a tube (prepared with RNAlater®) and ship at room temperature

What Does MMDx Assess?

**Rejection related:**
- Risk of T-cell mediated rejection (TCMR)
- Risk of Antibody-mediated rejection (ABMR)

**Injury & non-rejection related disease:**
- Acute and chronic injury
- Atrophy fibrosis
- Arterial hyalinsosis

Reducing the Economic Impact of Biopsy Testing

According to a study on the economic impact of molecular and histological biopsy testing⁴, the application of MMDx Kidney along with histological assessment can improve the diagnosis of graft dysfunction and may even produce cost savings in rejection-related treatment.

By more accurate characterizing rejection, the gene expression profiling test may support reductions in costs associated with graft failure, such as hospitalization, dialysis and repeat transplantation.

The study suggests that the clinical use of MMDx Kidney has generated an estimated undiscounted savings of **$19,271 per test** over a five-year period, assuming one test per patient.
Current and Emerging Applications for Molecular Assessment

Research suggests that molecular assessment may be useful, or even necessary, to accurately estimate rejection and injury in transplanted organs⁵.

**MMDx Kidney**

In kidney patients with chronic active antibody-mediated rejection (caAMR) and a high degree of chronicity, molecular evidence of rejection has been used to track responses to immunosuppressive therapies and identify response to treatment, as evidenced by improved inflammation⁶.
MMDx Kidney (cont.)
Inflammation in areas of atrophy-fibrosis (i-IFTA) has shown to be associated with increased risk of failure in kidney biopsies. A recent study has concluded that i-IFTA in indication biopsies reflect current or ongoing parenchymal injury, either with TCMR or (more commonly) with concomitant ABMR⁷.

MMDx Kidney has demonstrated accuracy and reproducibility in kidney biopsy assessment with minimal inter-observer disagreement in reporting. As a result, MMDx may be particularly valuable in cases when pathology results are “borderline” or “suspicious”⁸.

MMDx Heart
MMDx has demonstrated an improved sensitivity for the detection of subclinical graft injury in heart patients⁷ and for the detection of ABMR⁷. Molecular assessment may also provide greater clarity for biopsies with high probability of molecular injury but no molecular rejection, a state that can often be misdiagnosed as rejection by histology⁹.

MMDx Heart: Sample Report

| Patient Information | Clinical Interpretation | Summary of Molecular Changes (injury, rejection, scores) |

| Visualisation Relationship of biopsy to others in reference set | Indicates this biopsy |

| Molecular Microscope Diagnostic System MMDx | | |

| General | | |

<table>
<thead>
<tr>
<th>LIMS ID</th>
<th>Name</th>
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<tbody>
<tr>
<td>Sample Name</td>
<td>Patient Age at Bx</td>
</tr>
<tr>
<td>Date Reported (Y-M-D)</td>
<td>Biopsy Indication</td>
</tr>
<tr>
<td>Date Received (Y-M-D)</td>
<td>Estimated LVEF</td>
</tr>
<tr>
<td>Date of Transplant (Y-M-D)</td>
<td>DSA</td>
</tr>
<tr>
<td>Date of Biopsy (Y-M-D)</td>
<td>Clinical Diagnosis</td>
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<tr>
<td>Time of Biopsy Post-Tx</td>
<td>Histologic Diagnosis</td>
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</table>

**Pure molecular interpretation**

Abnormal cardiac transplant biopsy 4 years post-Tx. Extensive ABMR. No TCMR. Some parenchymal injury (QCMATs abnormal) and some parenchymal dedifferentiation (HT1s slightly abnormal). Compared to previous biopsy from January 29, 2020, this biopsy shows similar results.

Signed out by Dr. P.F. Halloran

<table>
<thead>
<tr>
<th>Proportion Rejection and Injury*</th>
<th>Model 1</th>
<th>NRI 0.00</th>
<th>TCMR/Injury 0.11</th>
<th>ABMR/Injury 0.89</th>
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<tr>
<td>Model 2</td>
<td>NRI 0.00</td>
<td>TCMR 0.07</td>
<td>ABMR 0.87</td>
<td>Injury 0.06</td>
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</table>

**Probable Rejection Diagnosis***

<table>
<thead>
<tr>
<th>Using Model 1</th>
<th>NRI 0.01</th>
<th>TCMR/Injury 0.03</th>
<th>ABMR/Injury 1.00</th>
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<tr>
<td>Using Model 2</td>
<td>NRI 0.02</td>
<td>TCMR 0.00</td>
<td>ABMR 1.00</td>
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**Principal Component Scores**

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<tr>
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<th>PC1</th>
<th>PC2</th>
<th>PC3</th>
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<tr>
<td></td>
<td>23.85</td>
<td>9.29</td>
<td>-4.39</td>
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NRI (Normality) = No Rejection or Injury. *Based on new algorithms accepted for presentation at the 2018 ISHLT meeting, April 11-14, Nice, France.
MMDx Lung

For lung patients, the histological assessment of transbronchial biopsies (TBB) offers limited reproducibility and presents considerable risk. However, evidence indicates molecular assessment with MMDx is a promising diagnostic solution for mucosal biopsies, a method that is much safer but not histologically interpretable.10

INTERLUNG Study: Molecular Diagnostic Report (Mucosal Biopsy, Third Bifurcation)

FOR RESEARCH PURPOSES ONLY. Report Version 4.02

General Information

<table>
<thead>
<tr>
<th>Name</th>
<th>Date Reported (Y-M-D)</th>
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<tr>
<td>Patient Age at Biopsy</td>
<td>Date Received (Y-M-D)</td>
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<tr>
<td>Patient ID</td>
<td>Date of Transplant (Y-M-D)</td>
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<tr>
<td>Sample Name</td>
<td>Date of Biopsy (Y-M-D)</td>
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<td>Biopsy Number</td>
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Clinical Information

<table>
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<th>Time of Biopsy Post-Tx</th>
<th>Biopsy Indication</th>
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Pure Molecular Interpretation

Relatively healthy 3BMB 1 year and 174 days post-Tx. No rejection (TCMR). Note agreement with TBB. (The relationship between the rejection archetype scores and actual rejection status is unclear and is the subject of the ongoing INTERLUNG study.)

Proportion Rejection and Injury

<table>
<thead>
<tr>
<th></th>
<th>Normal 0.65</th>
<th>Rejection 0.00</th>
<th>Sampling Heterogeneity 0.06</th>
<th>Late 0.24</th>
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<tr>
<td>PC1 score (x-axis)</td>
<td>-0.59</td>
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</table>

Visualization

Relationship of biopsy to others in reference set

Indicates this biopsy

MMDx Lung: Sample Report
The MMDx Process

Ordering Information
- Click "Specimen Kit Ordering"
- Complete ordering form and click "Order"
- A Specimen Kit will be delivered to your center

Specimen Kit Includes:
- Instructions
- Specimen tube and labels
- Return containers and labels

Specimen Handling
- Unpack your Specimen Kit and instructions.
- Place biopsy (Kidney: 3-5 mm of biopsy or portion of core) immediately from the needle or bite (Heart and Lung: 2 bites) in specimen tube provided in the kit. Washes will destroy the sample; please refrain from applying formalin, saline, or any other washes.
- Pack and ship. Pack samples and ship to address on the label provided in the kit.

Biopsy Results
- Results are available within 1-2 days after receipt of sample.
- Upon receipt of your sample, an account will be created for you on a secure client portal.
- You will receive an email notification once the report is available on the portal.

Client Services Assistance
- Assist with result interpretation/consultation
- Specimen requirements and handling
- Requisition completion
- Report status
- Client supplies
- Cost and billing

Service Lab & Billing Information
Kashi Clinical Laboratories, Inc.
Portland, Oregon
Phone: (877) 879-1815 or (503) 206-4989
Fax: (503) 206-6939

Hours of Operation
Monday – Friday: 7:00 am – 7:00 pm (PT)
Weekend and Holidays: on-call coverage

Sales & Technical Support
Email: 1lambda-mmdx@thermofisher.com
Website: go.1lambda.com/mmdx

One Lambda | A Thermo Fisher Scientific Brand
22801 Roscoe Blvd, West Hills, CA 91304, USA
TEL: 747.494.1000
FAX: 747.494.1001

International: Contact your local distributor
References


To learn how you can incorporate MMDx into your clinical practice, contact us at 1lambda-mmdx@thermofisher.com or visit go.1lambda.com/mmdx.