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MMDx Kidney, Heart & Lung

Personalized Transplant Care Through Precision Medicine

Molecular Microscope® Diagnostic System MMDx

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 score[1] 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.

A New Era of Precision Medicine

MMDx combines gene expression technology with the power of big data to deliver objective and reproducible transplant biopsy assessments.

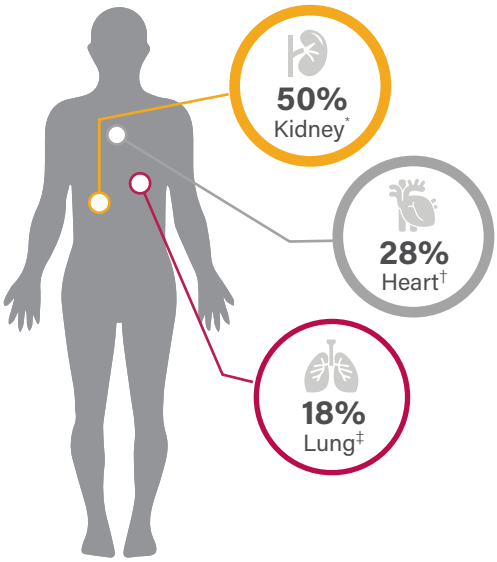
The MMDx algorithm compares the molecular features of the biopsy to those in an organ-specific reference set. The organ-specific reference sets were developed over the course of a decade and consist of over 1600 kidney samples, 1000 heart samples, 600 transbronchial biopsies (TBB) lung samples, and 300 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 TCMR[2]. Likewise, a mere 18% agreed on a TCMR diagnosis for a single lung sample[3] and 50% were in agreement after reviewing the same kidney sample[1].

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 hyalinosis

Reducing the Economic Impact of Biopsy Testing

According to a study on the economic impact of molecular and histological biopsy testing[4], 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 a 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 organs[5].

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 inflammation[6].

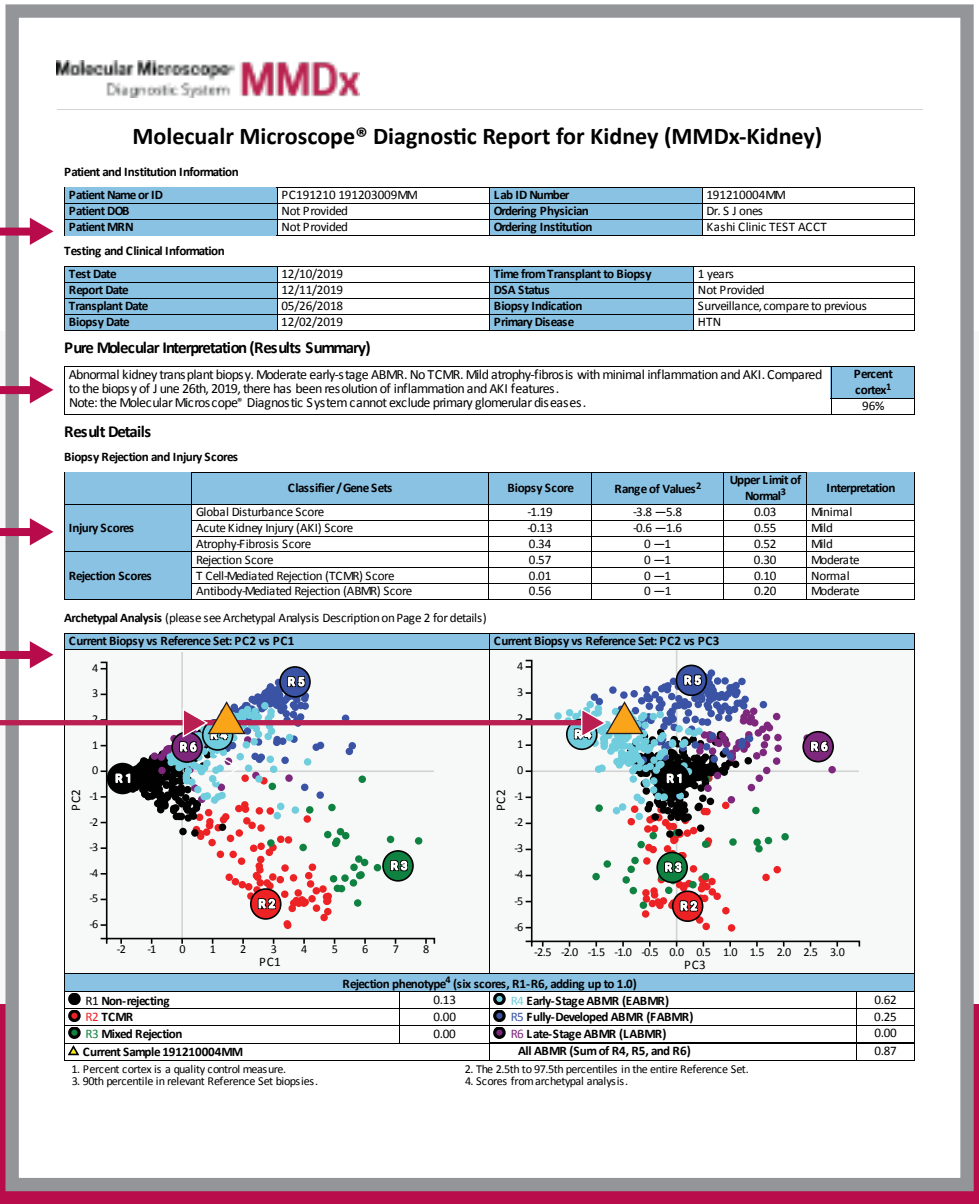
Patient Information

Clinical Interpretation

Summary of Molecular Changes (injury, rejection, scores)

Visualization Relationship of biopsy to others in reference set

Indicates this biopsy



Molecular Microscope® Diagnostic System MMDx

Molecualr Microscope® Diagnostic Report for Kidney (MMDx-Kidney)

Patient and Institution Information

Patient Name or ID	PC191210 191203009MM	**Lab ID Number**	191210004MM
Patient DOB	Not Provided	**Ordering Physician**	Dr. S J ones
Patient MRN	Not Provided	**Ordering Institution**	Kashi Clinic TEST ACCT

Testing and Clinical Information

Test Date	12/10/2019	**Time from Transplant to Biopsy**	1 years
Report Date	12/11/2019	**DSA Status**	Not Provided
Transplant Date	05/26/2018	**Biopsy Indication**	Surveillance, compare to previous
Biopsy Date	12/02/2019	**Primary Disease**	HTN

Pure Molecular Interpretation (Results Summary)

Abnormal kidney transplant biopsy. Moderate early-stage ABMR. No TCMR. Mild atrophy-fibrosis with minimal inflammation and AKI. Compared to the biopsy of June 26th, 2019, there has been resolution of inflammation and AKI features. Note: the Molecular Microscope® Diagnostic System cannot exclude primary glomerular diseases.	**Percent cortex[1]** 96%

Result Details

Biopsy Rejection and Injury Scores

	Classifier / Gene Sets	Biopsy Score	Range of Values[2]	Upper Limit of Normal[3]	Interpretation
Injury Scores	Global Disturbance Score	-1.19	-3.8 —5.8	0.03	Minimal
	Acute Kidney Injury (AKI) Score	-0.13	-0.6 —1.6	0.55	Mild
	Atrophy-Fibrosis Score	0.34	0 —1	0.52	Mild
Rejection Scores	Rejection Score	0.57	0 —1	0.30	Moderate
	T Cell-Mediated Rejection (TCMR) Score	0.01	0 —1	0.10	Normal
	Antibody-Mediated Rejection (ABMR) Score	0.56	0 —1	0.20	Moderate

Archetypal Analysis (please see Archetypal Analysis Description on Page 2 for details)

Rejection phenotype[4] (six scores, R1-R6, adding up to 1.0)			
R1 Non-rejecting	0.13	R4 Early-Stage ABMR (EABMR)	0.62
R2 TCMR	0.00	R5 Fully-Developed ABMR (FABMR)	0.25
R3 Mixed Rejection	0.00	R6 Late-Stage ABMR (LABMR)	0.00
Current Sample 191210004MM		All ABMR (Sum of R4, R5, and R6)	0.87

1. Percent cortex is a quality control measure.
2. The 2.5th to 97.5th percentiles in the entire Reference Set.
3. 90th percentile in relevant Reference Set biopsies.
4. Scores from archetypal analysis.

MMDx Kidney: Sample Report

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 ABMR[7].

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 patients[7] and for the detection of ABMR[7]. 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 histology[9].

Patient Information

Clinical Interpretation

Summary of Molecular Changes (injury, rejection, scores)

Visualization Relationship of biopsy to others in reference set

Indicates this biopsy

Molecular Microscope® Diagnostic System **MMDx**

General			
LIMS ID		Name	
Sample Name		Patient Age at Bx	
Date Reported (Y-M-D)		Biopsy Indication	
Date Received (Y-M-D)		Estimated LVEF	
Date of Transplant (Y-M-D)		DSA	
		Clinical Diagnosis	
Date of Biopsy (Y-M-D)		Histologic	
Time of Biopsy Post-Tx		Diagnosis	

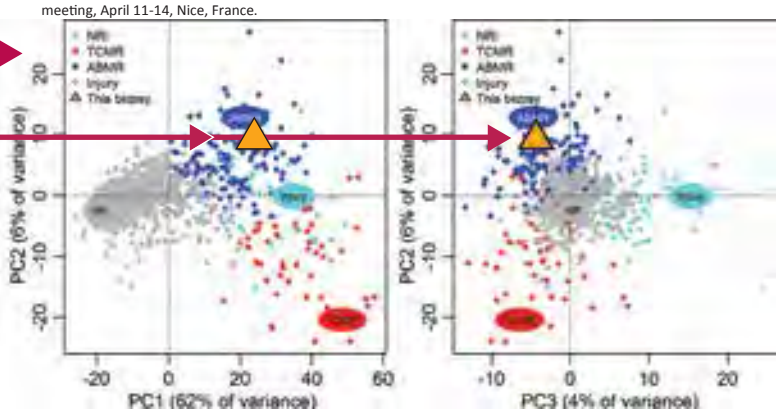
Pure molecular interpretation

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

Proportion Rejection and Injury*	Model 1	NRI	0.00	TCMR/Injury	0.11	ABMR/Injury	0.89		
	Model 2	NRI	0.00	TCMR	0.07	ABMR	0.87	Injury	0.06
Probable Rejection Diagnosis*	Using Model 1	NRI	0.01	TCMR/Injury	0.03	ABMR/Injury	1.00		
	Using Model 2	NRI	0.02	TCMR	0.00	ABMR	1.00		
Principal Component Scores				PC1	23.85	PC2	9.29	PC3	-4.39

NRI (Normalness) = No Rejection or Injury. *Based on new algorithms accepted for presentation at the 2018 ISHLT meeting, April 11-14, Nice, France.



MMDx Heart: Sample Report

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].

Patient Information

Clinical Interpretation

Summary of Molecular Changes (injury, rejection, scores)

Visualization Relationship of biopsy to others in reference set

Indicates this biopsy

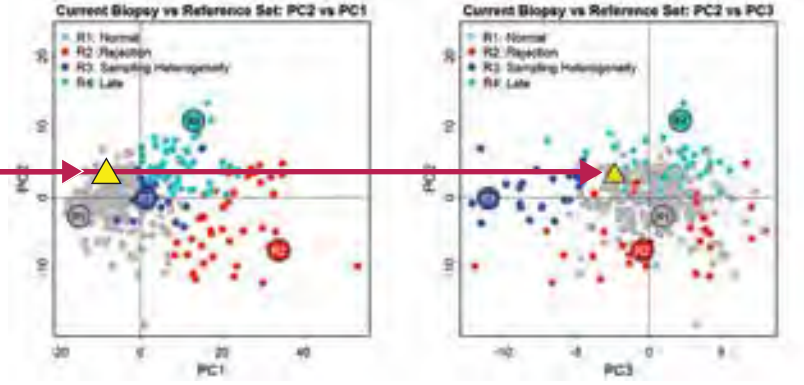
Molecular Microscope® Diagnostic System **MMDx**

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

General Information			
Name		Date Reported (Y-M-D)	
Patient Age at Biopsy		Date Received (Y-M-D)	
Patient ID		Date of Transplant (Y-M-D)	
Sample Name		Date of Biopsy (Y-M-D)	
Biopsy Number		Pieces processed	
Clinical Information			
Time of Biopsy Post-Tx		Biopsy Indication	
DSA Status		Clinical Dx	
Infection			

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 states is unclear and is the subject of the ongoing INTERLUNG study.)*

Proportion Rejection and Injury							
Normal	0.68	Rejection	0.00	Sampling Heterogeneity	0.08	Late	0.24
PC1 score (x-axis)	-8.59						



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

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TEL: 747.494.1000
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* Reeve J, et al. Am J Transplant 2013.

† Crespo-Leiro MG, et al. Transplant 2012.

‡ Arcasoy SM, et al. Am J Transplant 2011.

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

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