CEDIA® Mycophenolic Acid Assay

Thermo SCIENTIFIC

IVD **For In Vitro Diagnostic Use**

Rx Only

REF 100276

Intended Use

The CEDIA® Mycophenolic Acid (MPA) Assay is an in vitro diagnostic medical device intended for the quantitative measurement of mycophenolic acid in human plasma using automated clinical chemistry analyzers as an aid in the management of mycophenolic acid therapy in renal and cardiac transplant patients.

Summary and Explanation of the Test

Mycophenolic acid (MPA), metabolized from pro-drug mycophenolate mofetil (MMF, CellCept®) or mycophenolate sodium, is widely used for the prevention of rejection in patients receiving renal, heart, or liver transplants[1-5]. After administration, MMF and mycophenolate sodium are rapidly and extensively absorbed and hydrolyzed to MPA[1-4]. Biochemically, MPA is a potent and specific inhibitor of inosine-monophosphate dehydrogenase (IMPDH), an enzyme for the de novo purine synthesis used by B and T lymphocytes[1-6]. The inhibition of IMPDH by MPA suppresses B and T cell proliferation due to their dependency on de novo purine synthesis and thus results in immunosuppression. At clinically relevant concentrations, MPA is about 97% bound to human serum albumin with low dissociation constant at 13 µM[3, 7-8]. In patients, MPA is further metabolized by UDP-glucuronosyl transferase mainly to MPAG, the phenolic glucuronide of MPA, which is pharmacologically inactive[1-3] and, to a lesser extent, to acyl glucuronide of MPA (AcMPAG). There is a broad inter-patient variation of the ratio of AcMPAG to MPA[9-11] that may be affected by co-admnistered drugs, sampling time or other factors. The molar ratio of AcMPAG to MPA based on AUC was shown to be about 17-20% by Tedesco-Silva et al. (26-31% by weight)[9] and about 10% by Shipkova et al. (13-17% by weight)[10]. A ratio of 5.7-15.4% was observed by Kuypers et al.[11]. Monitoring of MPA may be important for effective use of the drug and for minimizing adverse side effects in patients[1, 4].

The CEDIA MPA Assay uses recombinant DNA technology (US Patent No. 4708929) to produce a unique homogenous enzyme immunoassay system[12]. The assay is based on the enzyme β-galactosidase, which has been genetically engineered into two inactive fragments termed enzyme donor (ED) and enzyme acceptor (EA). These fragments spontaneously re-associate to form fully active enzymes that, in assay format, cleave a substrate, generating a color change that can be measured spectrophotometrically.

In the assay, analyte in the specimen competes with analyte conjugated to ED of β-galactosidase for limited numbers of antibody binding sites. If analyte is present in the sample, it binds to the antibody leaving the ED conjugate free to form active enzymes with the EA. If analyte is not present in the sample, the antibody binds to analyte conjugated to ED, inhibiting the reassociation of ED to EA, and no active enzyme is formed. The amount of active enzyme formed and resultant absorbance change are directly proportional to the amount of drug present in the sample.

Reagents/Calibrators

1 **EA Reconstitution Buffer:** Contains TES {N-[Tris (hydroxymethyl) methyl]-2-aminoethane-sulfonic Acid}, anti-MPA polyclonal antibodies, stabilizer and preservative (1 x 26 mL).

1a **EA Reagent:** Contains 0.118 g/L Enzyme Acceptor (microbial), buffer salts, and preservative (Lyophilized).

2 **ED Reconstitution Buffer:** Contains potassium phosphate, detergent, and preservative (1 x 11 mL).

2a **ED Reagent:** Contains 58 µg/L MPA conjugated Enzyme Donor (microbial), 3.0 g/L chlorophenol red-β-D-galactopyranoside, stabilizers, and preservative (Lyophilized).

Additional Materials Provided:

Two (2) empty 20 mL bottles.

Additional Materials Required (but not provided):

REF	Kit Description
100277	CEDIA® Mycophenolic Acid Calibrator Kit
100278	MAS® Mycophenolic Acid Control 1 Kit
100279	MAS Mycophenolic Acid Control 2 Kit
100280	MAS Mycophenolic Acid Control 3 Kit

Automated clinical chemistry analyzer

⚠ Precautions and Warnings

Exercise the normal precautions required for handling all laboratory reagents.

CAUTION: Materials of human origin, used in formulation of MAS MPA controls, were tested for HIV1 and 2, Hepatitis B and Hepatitis C by FDA approved methods, and the findings were negative. However, as no test method can rule out the potential risk of infection with absolute certainty, the material must be handled as though infectious according to OSHSA standards on blood borne pathogens. In the event of exposure, the directives of the responsible health authorities should be followed.

DANGER: Powder reagent contains ≤56% w/w bovine serum albumin (BSA), ≤2.0% w/w sodium azide. Liquid reagent contains ≤1.0% bovine serum, ≤0.3% sodium azide, ≤0.1% drug-specific antibody and ≤2.0% Antisera (Goat).
H317 - May cause allergic skin reaction.
H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.
EUH032 - Contact with acids liberates very toxic gas.

Avoid breathing dust/mist/vapors/spray. Contaminated work clothing should not be allowed out of the workplace. Wear protective gloves/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. If on skin: Wash with plenty of soap and water. IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing. If skin irritation or rash occurs: Get medical advice/attention. If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. Wash contaminated clothing before reuse. Dispose of contents/ container to location in accordance with local/regional/national/international regulations.

Reagent Preparation

Refer to the specific instrument application sheet for assay parameters. Prepare the following solutions using refrigerated (2-8ºC) reagents and buffers. Remove the kit from refrigerated storage immediately prior to preparation of the working solutions.

In the case of accidental spill, clean and dispose of material according to your laboratory's SOP, local, and state regulations.

In the case of damaged packaging on arrival, contact your technical support representative (refer to back page of this PI).

Prepare reagents in the following order to minimize possible contamination.

R2 Enzyme donor solution: Connect Bottle 2a (ED Reagent) to Bottle 2 (ED Reconstitution Buffer) using one of the enclosed adapters. Mix by gentle inversion, ensuring that all the lyophilized material from Bottle 2a is transferred into Bottle 2. **Avoid the formation of foam.** Detach Bottle 2a and adapter from Bottle 2 and discard. Cap filled Bottle 2 and let stand approximately 5 minutes at room temperature (15-25ºC). Gently mix again and record the reconstitution date on the bottle label. Place the bottle directly into the reagent compartment of the analyzer or into refrigerated (2-8ºC) storage and let stand 15 minutes before use.

R1 Enzyme acceptor solution: Connect Bottle 1a (EA Reagent) to Bottle 1 (EA Reconstitution Buffer) using one of the enclosed adapters. Mix by gentle inversion, ensuring that all the lyophilized material from Bottle 1a is transferred into Bottle 1. **Avoid the formation of foam.** Detach Bottle 1a from adapter and discard. Cap filled Bottle 1 and let stand approximately 5 minutes at room temperature (15-25ºC). Gently mix again and record the reconstitution date on the bottle label. Place the bottle directly into the reagent compartment of the analyzer or into refrigerated (2-8ºC) storage and let stand 15 minutes before use.

If your analyzer cannot accommodate the size of bottle 1, two (2) empty smaller trapezoidal style bottles have been included. Decant the contents of the larger bottle 1 into each of the 2 smaller bottles dividing the volume equally between the two bottles.

Note 1: The components supplied in this kit are intended for use as an integral unit. Do not mix components from different kits lots of the CEDIA® MPA Assay or other CEDIA kits.

Note 2: Avoid cross contamination of reagents by matching reagent caps to the proper reagent bottle. The R2 solution (ED Reagent) should be yellow-orange in color. A red or purple-red color indicates that the reagent has been contaminated and must be discarded.

Note 3: The R1 and R2 solutions must be at the reagent compartment storage temperature of the analyzer before performing the assay. Refer to the analyzer specific application sheet for additional information.

Note 4: To ensure reconstituted EA reagent stability, protect from prolonged continuous exposure to bright light.

Storage Condition

Store components at proper temperature. **DO NOT FREEZE.** For stability of the unopened components, refer to the box or bottle labels for the expiration date.

R1 Solution: 60 days refrigerated or at 2-8ºC

R2 Solution: 60 days refrigerated or at 2-8ºC

Sample Collection and Handling

Use Na_2EDTA or K_2EDTA plasma samples. Care should be taken to preserve the integrity of the specimen from the time of collection until performance of the assay. Specimens should be labeled with both the time of blood collection as well as the last drug administration. Specimens should be capped and assayed within 14 days when stored at 2-8ºC (acceptance criteria of +/- 10% recovery) or within 5 months when stored at ≤ -20ºC[4,13]. Avoid repeated freezing and thawing. Do not induce foaming of samples.

Barcode Usage: Reagent labels have a dedicated system barcode that most analyzers will ignore if unrecognized. If the analyzer returns an error code, overlay the barcode with solid-colored tape. Contact Technical Services for assistance if needed.

Assay Procedure

Calibration

The CEDIA MPA Assay produces a standard curve using the appropriate CEDIA MPA Calibrators. Prior to assaying patient specimens, validate assay calibration by testing control(s) with recovery ranges established for the CEDIA MPA Assay.

Note: A calibrator value assignment card is included in each CEDIA MPA Calibrator kit. Before using a new kit, check your chemistry parameters to ensure that the calibrator concentrations match the values printed on the value assignment card.

Calibration Frequency

Recalibration is recommended

- As required following your laboratory's quality control procedures, and
- After reagent bottle change
- After calibrator or reagent (kit) lot change
- After performance of monthly instrument maintenance

Reportable Range

The reportable range for the CEDIA MPA Assay is 0.3 to 10 µg/mL.

Out of Range Samples

Specimens quantifying >10 µg/mL can be reported as "concentration >10 µg/mL" or diluted one part original sample with one part negative calibrator, and re-assayed. The value obtained on re-assay should be derived as follows:

Actual Value = 2 x diluted value

Specimens with a result below the functional sensitivity of the assay should be reported as <0.3 µg/mL.

Quality Control and Calibration

Each laboratory should establish its own control frequency. Good laboratory practice suggests that at least two concentrations (e.g., low and high medical decision points) of quality control be tested each day patient samples are assayed and each time calibration is performed. Monitor the control values for any trends or shifts. If any trends or shifts are detected, or if the control does not recover within the specified range, review all operating parameters. Contact Microgenics Technical Support for further assistance and recommendations for suitable control material. All quality control requirements should be performed in conformance with local, state and/or federal regulations or accreditation requirements.

Note: Reassess control targets and ranges following a change of reagent (kit) lot.

Limitations-Interference Substances

Performance characteristics for the CEDIA® MPA Assay have not been established for body fluids other than human plasma.

Acceptance Criteria: Regarding interference information below, performance was deemed acceptable (no significant interference) when MPA recovery was ± 0.3 µg/mL at initial concentrations of < 3 µg/mL or ± 10% of initial concentrations of > 3 µg/mL.

Icterus (jaundice): No significant interference from unconjugated Bilirubin up to a concentration of 20 mg/dL.

Lipemia: No significant interference from Triglycerides up to a concentration of 1600 mg/dL and from Cholesterol up to 400 mg/dL.

Total Protein: No significant interference from total protein up to 10 g/dL.

Rheumatoid factor: No significant interference from Rheumatoid Factor up to a concentration of 2000 IU/mL.

Hemoglobin: No significant interference from Hemoglobin up to a concentration of 1000 mg/dL.

EDTA concentration: Plasma samples collected in the tube containing EDTA anticoagulant were recommended for MPA testing[15]. No significant interference was observed with the normal amount of samples collected in VACUTAINER® (purple stopper). However, if the sample collected fills less than 1/3 of the tube, the resulting high EDTA concentration will cause a relative overestimation of MPA concentration.

Other anticoagulants: Although plasma containing EDTA anticoagulant is the preferred matrix for MPA measurement, heparin was tested for interference. No significant interference was found from this anticoagulant. For all anticoagulants, no samples collected should fill less than 1/3 of the tube for CEDIA MPA assay since it tends to give higher recovery of MPA.

Antibodies to E. coli β-galactosidase: The incidence of patients having antibodies to E. coli β-galactosidase is extremely low. However, some samples containing such antibodies can produce erroneously high concentrations of MPA, which may be inconsistent with the patient's clinical profile. If you suspect this occurrence, please contact Microgenics Technical Service for assistance.

Limitations-Assay Difference and Variation

Different immunoassays may yield variable results for the same sample due to assay-specific variations in metabolite cross reactivity. Patients with impaired clearance (e.g.,renal insufficiency) may show the most variation. For such patients, use of this assay may be supported with a chromatographic method that is specific for MPA. Given the potential bias or scatter about the comparison of the CEDIA MPA Assay and HPLC for detection of MPA in specimens, it is important for each laboratory to establish its therapeutic range based on its own patient population.

Limitation-AcMPAG Cross-reactivity

The assay has a cross-reactivity of 158% to AcMPAG which may cause a positive bias as compared to methods, such as LC-MS/MS, that do not have cross-reactivity. The bias relative to LCMS for any individual patient sample is related in part to the concentration of AcMPAG in that particular sample.

Expected Values

The optimal therapeutic range for MPA in plasma has not been fully established. In addition, optimal patient MPA concentration ranges may vary depending on the specific assay and its metabolite cross-reactivities, (See cross-reactivity section, below, for observed cross-reactivities with this assay). Therefore, optimal ranges should be established for each commercial test and values obtained with different assay methods cannot be used interchangeably, nor should correction factors be applied. Laboratories should include identification of the assay used on patient reports in order to aid in interpretation of results.

Optimal ranges depend upon transplant type and co-administered drugs, as well as the patient's clinical state, individual differences in sensitivity to immunosuppressive and toxic effects of MPA, time post-transplant and a number of other factors. Individual MPA values cannot be used as the sole indicator for making changes in treatment regimen and each patient should be thoroughly evaluated clinically before changes in treatment regimens are made. Each institution should establish the optimal ranges based on the specific assay used and other factors relevant to its patient population.

Examples of literature discussing observed optimal ranges for MPA are included in the references[16-20]. Features such as the specific assays, specific clinical characteristics, and sampling times in these references should be noted.

Specific Performance Characteristics

Typical performance data for the CEDIA MPA Assay on the Hitachi 917 analyzer are provided below[10]. Results obtained in individual laboratories may differ from these data. For additional analyzer specific performance data, refer to the analyzer specific application protocol or call Microgenics Technical Support for assistance.

Precision

Within-run and total-run precision (reproducibility) studies were conducted using specimens from transplant patients taking MMF, plasma spiked with MPA and controls. Pool 2 was made of specimens from transplant patients and pools 1 and 3 are MPA negative plasma specimens spiked with MPA. All samples were assayed in a total of 21 runs over 11 days using the modified protocol from CLSI (EP5A). Calibration was performed for each run. Results are presented in the table below.

Within and Total Assay Precision (Reproducibility)

			Within-run		Total-run	
Sample	**N**	**Mean**	**SD**	**CV%**	**SD**	**CV%**
Patient Pool 1	126	1.0	0.06	5.6	0.08	7.7
Patient Pool 2	126	2.4	0.07	2.8	0.09	4.0
Patient Pool 3	126	6.0	0.09	1.5	0.14	2.3
Control 1	126	1.1	0.06	5.5	0.10	9.5
Control 2	126	2.7	0.06	2.2	0.13	4.8
Control 3	126	5.9	0.12	2.0	0.20	3.3

Linearity

To assess assay linearity, a high patient plasma sample was diluted using an MPA-free plasma sample to produce a series of samples across the dynamic range of the assay. Each sample was tested in replicates of 5 and the mean value was used as measured results. The percent recovery was determined by dividing the observed MPA concentration by the expected concentration. The expected concentrations were determined using the highest concentration tested times a dilution factor.

Diluted Samples	Expected Value (µg/mL)	Measured Value (µg/mL)	Recovery (%)
Level 1	9.8	9.8	-
Level 2	7.4	7.4	100
Level 3	4.9	4.9	100
Level 4	3.4	3.3	97
Level 5	2.5	2.3	92
Level 6	1.0	0.9	90
Level 7	0.5	0.4	80
Level 8	0.0	0.0	-

Recovery

To assess assay recovery, MPA was added to normal MPA-free plasma and transplant patient specimens containing MPA. Sample was tested in 21 replicates for normal plasma matrix and 5 replicates for transplant sample matrix. Recovery was calculated by dividing the observed concentration of each sample by the expected concentration of added MPA plus MPA originally present in the samples.

MPA-free Plasma

Expected Value (µg/mL)	Measured Value (µg/mL)	Recovery (%)
0.0	0.0	-
0.5	0.5	100
1.0	0.9	90
2.5	2.5	100
3.5	3.2	91
7.0	6.5	93

Tx Patient Plasma

Expected Value (µg/mL)	Measured Value (µg/mL)	Recovery (%)
Patient 1		
0.5	0.5	-
1.0	1.0	100
2.5	2.6	104
Patient 2		
2.4	2.4	-
3.4	3.3	97
6.9	6.8	99

Specificity

Different concentrations of MPA glucuronide metabolites were added to plasma containing MPA for the cross-reactivity test. The estimated cross-reactivity of the compounds was calculated using the formula and the results are shown in the table below.

$$\frac{\text{(concentration measured - control concentration)} \times 100\%}{\text{cross-reactant concentration tested}}$$

Cross-Reactivity with MPA Metabolites

Compound	Concentration Tested (µg/mL)	Cross-Reactivity (%)
7-O-Glucuronide MPA (MPAG)	1000	0.0
Acyl glucuronide MPA (AcMPAG)	10.0 3.0 1.8 0.9 0.3	164.0 170.0 144.4 177.8 133.3 Average 158

Note: Due to the cross-reactivity to AcMPAG in the CEDIA MPA assay, it is anticipated that there will be a potential positive bias between CEDIA MPA assay and LC-MS/MS.

Other immunosuppressants were tested for the cross reactivity to the assay. The compounds listed below showed no cross-reactivity at the tested concentration in CEDIA MPA assay.

Compounds	Tested Concentration, µg/mL
Sirolimus	0.3
Tacrolimus	0.3
Cyclosporine	10

Common drugs were tested in the MPA-free plasma for cross reactivity to the assay. The compounds listed below showed no cross-reactivity at the tested concentration in CEDIA MPA assay.

Compounds	Tested Concentration, µg/mL
Acetaminophen	100
N-acetylprocainamide	100
Acyclovir	100
Amikacin	100
Amphotericin B	50
Ampicillin	100
Azathioprine	100
Carbamazepine	100
Chloramphenicol	100
Cimetidine	100
Ciprofloxacin	100
Digoxin	10
Digitoxin	10
Disopyramide	100
Erythromycin	100
Fluconazole	100
Flucytosine	100
Furosemide	100
Gancyclovir	100
Gentamicin	100
Hydrocortisone	100
Itraconazole	100
Kanamycin A	100
Kanamycin B	100
Ketoconazole	100
Lidocaine	100
Methylprednisolone	100
Morphine	100
Penicillin	100
Phenobarbital	100
Phenytoin	100
Prazosin	100
Prednisolone	100
Prednisone	100
Procainamide	100
Quinidine	100
Rifampicin	60
Sodium Salicylate	50
Spectinomycin	100
Streptomycin	100
Theophylline	100
Tobramycin	100
Triamterene	100
Valproic Acid	100
Vancomycin	100
Verapamil	100

Least Detectable Dose

LDD is defined as the lowest concentration that can be differentiated from zero with 95% confidence. Twenty-one MPA negative plasma specimens were tested for least detectable dose (LDD) and the LDD is 0.2 µg/mL.

Functional Sensitivity

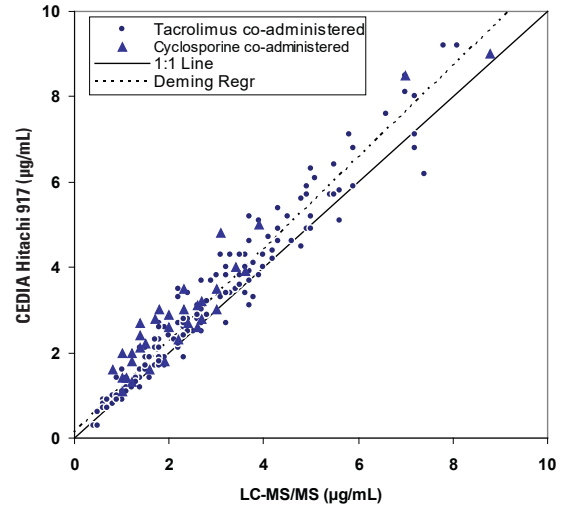
The functional sensitivity, defined as the lowest drug concentration that gives a coefficient of variation (CV%) of < 20%, is 0.3 µg/mL for the CEDIA MPA Assay. At this concentration, there is approximately 0.01 µg/mL bias, 104% recovery, and 17.6% CV.

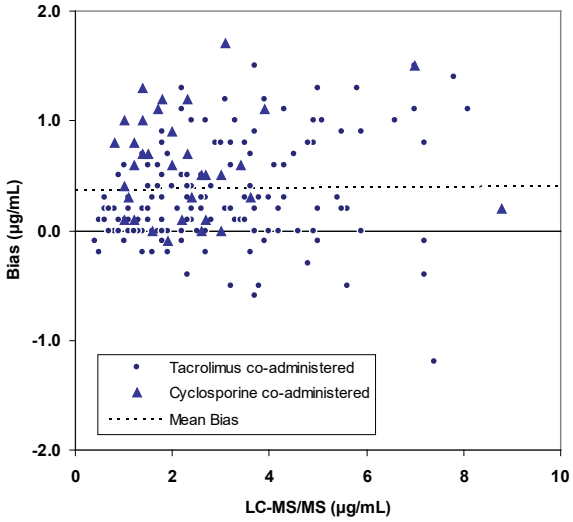
Method Comparison

A total of 188 pre-dose samples from adult transplant patients receiving mycophenolate mofetil or mycophenolate sodium therapy were tested in a method comparison study using LC-MS/MS as the reference method. The table below summarizes the results of the study showing separate analysis by transplant type and together using EP Evaluator. In the regression method column, the slope and intercept results are presented with 95% confidence intervals in parentheses.

Sample	N	Regression Method		r
Plasma Heart	96	Least Square slope Least Square intercept	1.114 (1.061 to 1.166) 0.20 (0.05 to 0.36)	0.9743
		Deming slope Deming intercept	1.147 (1.094 to 1.200) 0.12 (-0.04 to 0.28)	
Plasma Kidney	92	Least Square slope Least Square intercept	1.127 (0.974 to 1.080) 0.16 (-0.03 to 0.36)	0.9711
		Deming slope Deming intercept	1.060 (1.006 to 1.113) 0.06 (-0.13 to 0.25)	
Plasma All	188	Least Square slope Least Square intercept	1.054 (1.015 to 1.092) 0.22 (0.09 to 0.34)	0.9698
		Deming slope Deming intercept	1.089 (1.051 to 1.128) 0.12 (-0.01 to 0.25)	

The majority of patients had tacrolimus co-administered (n=153), shown as circles in the graphs below. The others had cyclosporine co-administered (n=34), shown as triangles in the graphs below.





N = 188
Mean (Y-X) = 0.37
SD (Y-X) = 0.47
1.96 SD = 0.92
Mean + 1.96 SD = 1.29
Mean – 1.96 SD = -0.55

References

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Glossary:

http://www.thermofisher.com/symbols-glossary

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