

Leukotriene E4, 24 Hour, Urine

## **Overview**

## **Useful For**

Aiding in the evaluation of patients at-risk for mast cell activation syndrome (eg, systemic mastocytosis, IgE-mediated allergies, or aspirin-exacerbated respiratory disease) using 24-hour urine collections

## **Profile Information**

Test Id	Reporting Name	Available Separately	Always Performed
LTE4T	Leukotriene E4, 24 Hr, U	No	Yes
CRT2F	Creatinine, 24 HR, U	No	Yes

## **Special Instructions**

Urine Preservatives-Collection and Transportation for 24-Hour Urine Specimens

## **Highlights**

Quantitation of urinary metabolites of histamine, prostaglandin D2, and leukotriene E4 may provide significant clues for the diagnosis and management of symptomatic patients with both clonal and nonclonal mast cell activation syndromes. The presence of 1 or more elevated levels of these biomarkers in urine greatly narrows diagnostic possibilities for causes of symptoms; informs the practitioner what specific metabolic pathways are involved; and targets the treatment in a specific, personalized fashion.

### **Method Name**

LTE4T: Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

CRT2F: Enzymatic Colorimetric Assay

## **NY State Available**

Yes

# Specimen

## Specimen Type

Urine

## Ordering Guidance

Random urine collections are preferred for patients with episodic symptoms, (eg, in the context of allergic reactions brought on by specific environmental factors or mast cell activation syndrome). For random urine collection, order RLTE4 / Leukotriene E4, Random, Urine.

# **Additional Testing Requirements**

For an optimal evaluation, testing for urinary leukotriene E4 should be accompanied with laboratory investigations for



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the presence of serum tryptase (TRYPT / Tryptase, Serum), urinary 2,3-dinor 11 beta-prostaglandin F2 alpha (23BPT / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, 24 Hour, Urine) and urinary *N*-methylhistamine (NMH24 / *N*-Methylhistamine, 24 Hour, Urine).

## **Necessary Information**

Specimen volume (in milliliters) and duration are required.

## **Specimen Required**

**Patient Preparation:** Patients taking 5-lipoxygenase inhibitor zileuton (Zyflo) may have decreased concentrations of leukotriene E4 (LTE4). If medically feasible, the patient should not take zileuton for 48 hours before specimen collection.

**Supplies:** Sarstedt Aliquot Tube, 5 mL (T914)

Container/Tube: Plastic vial Specimen Volume: 5 mL Collection Instructions:

- 1. Start collection within a few hours of symptom onset and collect urine for 24 hours
- 2. No preservative preferred
- 3. Aliquot urine into a plastic vial and send frozen.

**Additional Information:** See <u>Urine Preservatives-Collection and Transportation for 24-Hour Urine Specimens</u> for multiple collection.

## **Urine Preservative Collection Options**

**Note:** The addition of preservative or application of temperature controls **must occur within 4 hours of completion** of the collection.

Ambient (no additive)	No
Refrigerate (no additive)	Preferred
Frozen (no additive)	OK
50% Acetic Acid	OK
Boric Acid	OK
Diazolidinyl Urea	No
6M Hydrochloric Acid	No
6M Nitric Acid	No
Sodium Carbonate	OK
Toluene	No

## Specimen Minimum Volume

2 mL

## Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

## **Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Urine	Frozen (preferred)	28 days	
	Ambient	24 hours	



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Refrigerated	7 days	
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## Clinical & Interpretive

### **Clinical Information**

Leukotrienes (LT) are eicosanoids generated from arachidonic acid via the 5-lipoxygenase pathway. Leukotriene E4 (LTE4) is the stable end product of this pathway and, therefore, regarded as a biomarker of total cysteinyl leukotriene production.(1-3) Assessment of LTE4 in urine allows for noninvasive specimen collection and avoids artifactual formation of LT during phlebotomy. Generation of LTE4 occurs nonspecifically from active mast cells (MC), basophils, eosinophils, and macrophages and is modulated through a variety of mechanisms.(1) Elevated concentrations of LTE4 are associated with both clonal (primary) and nonclonal (secondary and idiopathic) MC activation syndromes (MCAS).(1-3) MCAS have been defined as a group of disorders in which patients experience symptoms precipitated by MC proinflammatory and vasoactive mediator release.(1) Some of these MC mediators contribute to physiologic processes and maintenance of tissue homeostasis.

Primary MCAS have clonal markers, such as the *KIT* Asp816Val variant or aberrant expression of CD25 or CD2 on MC. The 2 primary groups of MCAS are mastocytosis (cutaneous and systemic [SM]) and monoclonal MCAS. Patients with mastocytosis should fulfill the World Health Organization diagnostic criteria for this disorder. Diagnosis requires either the major plus one minor criterion or 3 minor criteria. (1,4,5)

The consensus diagnostic criteria for SM include:

Major criterion: Imaging of the multifocal infiltrates

Minor criteria:

- 1. Identifying morphological features of above 25% of MC from bone marrow biopsy
- 2. Detection of the point alteration at codon 816 in the KIT gene
- 3. CD2, CD25, and/or CD30 expression in MC
- 4. Persistently elevated serum tryptase (>20 ng/mL)

The 2 main nonclonal MCAS categories include secondary MCAS, for which there is a known trigger for MC activation (IgE-dependent and independent allergic reactions, atopic disorders, autoimmune processes), and idiopathic, in which the etiology for MC activation is undefined.(1-3,5-7) Based on consensus criteria, the diagnosis of MCAS can be established when typical clinical symptoms arising from recurrent (episodic) acute systemic MC activation (typically in the form of recurrent anaphylaxis in at least 2 organ systems) have been documented; MC-derived mediators increase substantially in serum or urine over the individual's baseline; and the symptoms respond to drugs blocking MC activation, MC mediators, mediator production, or mediator effects.(6)

A recently proposed diagnostic algorithm for the evaluation of patients with suspected MCAS considers 2 main diagnoses that may underlie severe forms of MC activation (anaphylaxis), namely, IgE-dependent allergies and clonal MC disorders.(1-3,5-7) A serum tryptase level, which has long been used in diagnosing these disorders, has several drawbacks, including the need to obtain acute and baseline specimens to fulfill diagnostic criteria. Furthermore, an increased baseline tryptase level has been reported in hereditary alpha tryptasemia, complicating the diagnostic possibilities.(1,3) In addition to the limitations of serum tryptase, there are reports of symptomatic patients with features of MC activation who do not meet all the criteria for MCAS but have elevated baseline mediator metabolites.(3,5,7) In these patients, there is evidence that their symptoms respond to drugs that target MC activation, the mediators released by MC, and/or the effects of these mediators. Based on these observations, validated



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biomarkers suggestive of MC activation, such as an increase in the histamine metabolite (*N*-methylhistamine) or the prostaglandin D2 metabolite (2,3-dinor 11 beta-prostaglandin F2 alpha), have been recommended for testing when tryptase is not available, or the result is inconclusive.(7)

With respect to urine LTE4, there is increasing clinical evidence for its use in patients at risk for aspirin intolerance in asthma (aspirin-exacerbated respiratory disease) and other forms of asthma.(8,9) For example, elevated LTE4 concentrations have been shown to correlate with traditional markers and represent a noninvasive approach to asthma phenotyping in patients with type 2 asthma mediated in part by MC and eosinophils.(9) In this study, increased urine LTE4 levels were associated with lower lung function and increased amounts of exhaled nitric oxide and eosinophil markers in blood, sputum, and urine in adult and adolescent patients with asthma. Based on these and other findings, there is interest for the use of therapeutics that target the production of inflammatory eicosanoids, such as LTE4, in the management of these diseases.(10-12)

#### Reference Values

**LEUKOTRIENE E4:** 

< or =104 pg/mg creatinine

### **CREATININE:**

<18 years: Not established Normal values mg per 24 hours: Males: 930-2955 mg/24 hours Females: 603-1783 mg/24 hours

## Interpretation

Elevated urinary leukotriene E4 concentrations above 104 pg/mg creatinine may be suggestive of mast cell activation syndrome if compatible features of disease are present.

## **Cautions**

Mast cell (MC) activation disorder is a heterogenous disease, and the absence of elevated LTE4 does not exclude the diagnosis of MC disease.

Increased excretion of LTE4 is nonspecific and should not be used alone to make a clinical diagnosis of a MC activation disease.

This assay measures both LTE4 and the 11-trans-LTE4 as markers of MC release.

### Clinical Reference

- 1. Weiler CR. Mast cell activation syndrome: Tools for diagnosis and differential diagnosis. J Allergy Clin Immunol Pract. 2020;8(2):498-506
- 2. Gulen T, Akin C, Bonadonna P, et al. Selecting the right criteria and proper classification to diagnose mast cell activation syndromes: A critical review. J Allergy Clin Immunol Pract. 2021;9(11):3918-3928
- 3. Butterfield JH. Nontryptase urinary and hematologic biomarkers of mast cell expansion and mast cell activation: Status 2022. J Allergy Clin Immunol Pract. 2022;10(8):1974-1984
- 4. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-1427
- 5. Valent P, Akin C, Hartmann K., et al. Updated diagnostic criteria and classification of mast cell disorders: A consensus



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proposal. Hemasphere. 2021;5(11):e646

- 6. Divekar R, Hagan J, Rank M, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. J Allergy Clin Immunol Pract. 2016;4(4):665-670
- 7. Valent P, Hartmann K, Bonadonna P, et al. Global classification of mast cell activation disorders: An
- ICD-10-CM-adjusted proposal of the ECNM-AIM Consortium. J Allergy Clin Immunol Pract. 2022;10(8):1941-1950
- 8. Kolmert J, Gomez C, Balgoma D, et al. Urinary leukotriene E(4) and prostaglandin D(2) metabolites increase in adult and childhood severe asthma characterized by type 2 inflammation. A clinical observational study. Am J Respir Crit Care Med. 2021;203(1):37-53
- 9. Hagan JB, Laidlaw TM, Divekar R, et al. Urinary leukotriene E4 to determine aspirin intolerance in asthma: A systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2017;5(4):990-997.e1. doi:10.1016/j.jaip.2016.11.004 10. Hayashi H, Fukutomi Y, Mitsui C, et al. Omalizumab for aspirin hypersensitivity and leukotriene overproduction in aspirin-exacerbated respiratory disease. A randomized controlled trial. Am J Respir Crit Care Med. 2020;201(12):1488-1498
- 11. Buchheit KM, Lewis E, Gakpo D, et al. Mepolizumab targets multiple immune cells in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2021;148(2):574-584
- 12. Buchheit KM, Sohail A, Hacker J, et al. Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2022;150(2):415-424

## **Performance**

## **Method Description**

Leukotriene E4:

The specimen and an internal standard are assayed by liquid chromatography tandem mass spectrometry. The analyte is detected by multiple-reaction monitoring. (Lueke AJ, Meeusen JW, Donato LJ, Gray AV, Butterfield JH, Saenger AK. Analytical and clinical validation of an LC-MS/MS method for urine leukotriene E4: A marker of systemic mastocytosis. Clin Biochem. 2016;49[13-14]:979-982)

#### Creatinine:

This enzymatic method is based on the determination of sarcosine from creatinine with the aid of creatininase, creatinase, and sarcosine oxidase. The liberated hydrogen peroxide is measured via a modified Trinder reaction using a colorimetric indicator. Optimization of the buffer system and the colorimetric indicator enables the creatinine concentration to be quantified both precisely and specifically.(Package insert: Creatinine plus ver 2. Roche Diagnostics; V15.0, 03/2019)

## PDF Report

No

## Day(s) Performed

Monday, Tuesday, Thursday

# Report Available

2 to 9 days

## Specimen Retention Time



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14 days

# **Performing Laboratory Location**

Mayo Clinic Laboratories - Rochester Superior Drive

## **Fees & Codes**

## **Fees**

- Authorized users can sign in to <u>Test Prices</u> for detailed fee information.
- Clients without access to Test Prices can contact <u>Customer Service</u> 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact <u>Customer Service</u>.

## **Test Classification**

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

## **CPT Code Information**

82542

# **LOINC®** Information

Test ID	Test Order Name	Order LOINC® Value
TLTE4	Leukotriene E4, 24 Hr, U	101115-4

Result ID	Test Result Name	Result LOINC® Value
603458	Leukotriene E4, U	101115-4
CR_AF	Creatinine, 24 HR, U	2162-6
TM10F	Collection Duration (h)	13362-9
VL8F	Urine Volume (mL)	3167-4
CRF24	Creatinine Concentration, 24 HR, U	20624-3