MAYO CLINIC LABORATORIES

Test Definition: 3A4Q

Cytochrome P450 3A4 Genotype, Varies

Overview

Useful For

Aids in determining therapeutic strategies for drugs that are metabolized by cytochrome P450 3A4, including atorvastatin, simvastatin, and lovastatin

This test is **not useful for** managing patients receiving fluvastatin, rosuvastatin, or pravastatin since these drugs are **not** metabolized appreciably by CYP3A4.

Special Instructions

- Informed Consent for Genetic Testing
- Pharmacogenomic Association Tables
- Multiple Genotype Test List
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) With Allelic Discrimination Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Testing is available as the single gene assay (this test) and as a part of a psychotropic or focused pharmacogenomics panel.

If multiple pharmacogenomic genotype testing is desired, order PGXQP / Focused Pharmacogenomics Panel, Varies.

If genotype testing for psychotropic medications is desired, order PSYQP / Psychotropic Pharmacogenomics Gene Panel, Varies.

Additional Testing Requirements

Most drugs metabolized by CYP3A4 are also metabolized by CYP3A5, but usually to a lesser extent, so testing of CYP3A5 may also be relevant and should be determined on a case by case basis. If CYP3A5 genotyping is needed, order 3A5Q / Cytochrome P450 *3A5* Genotype, Varies.

Specimen Required

Multiple genotype tests can be performed on a single specimen after a single extraction. See Multiple Genotype Test List in Special Instructions for a list of tests that can be ordered together.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.
Specimen Stability Information: Ambient (preferred) 9 days/Refrigerated 30 days

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies: Saliva Swab Collection Kit (T786)
Specimen Volume: One swab
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient 30 days

Specimen Type: Extracted DNA
Container/Tube: 2 mL screw top tube
Specimen Volume: 100 mcL (microliters)
Collection Instructions:
1. The preferred volume is 100 mcL at a concentration of 50 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
-Pharmacogenomics Test Request (T797)
-Cardiovascular Test Request (T724)
-Neurology Specialty Testing Client Test Request (T732)
-Therapeutics Test Request (T831)

Specimen Minimum Volume

Blood: 0.4 mL
Saliva: 1 swab

Reject Due To

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

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

CYP3A4 is a member of the *CYP3A* family of genes located on chromosome 7. The cytochrome P450 (CYP) 3A subfamily of enzymes is responsible for the metabolism of more than 50% of medications that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells, including some lipid-lowering drugs. The CYP3A4 enzyme activity is highly variable. Interindividual differences in enzyme expression may be due to several factors including: variable homeostatic control mechanisms, disease states that alter homeostasis, up- or down-regulation by environmental stimuli, and genetic variation.(1)

One variant, *CYP3A4*22* (c.522-191C>T), has been studied extensively. This variant affects hepatic expression of CYP3A4 and response to statin drugs. The *CYP3A4*22* allele is associated with reduced CYP3A4 activity, which may result in a better response to lipid-lowering drugs, such as simvastatin, atorvastatin, or lovastatin. However, reduced CYP3A4 activity may also be associated with statin-induced myopathy, especially for simvastatin. Studies show that in livers with the reference (wild-type) genotype (homozygous C or CC) the *CYP3A4* mRNA level and enzyme activity were 1.7- and 2.5-fold greater than in *CYP3A4*22* heterozygotes (CT) and homozygotes (TT), respectively. In 235 patients taking stable doses of drugs for lipid control, carriers of the T allele required significantly lower statin doses for optimal lipid control than did non-T carriers.(2) These results indicate that *CYP3A4*22* markedly affects expression of CYP3A4 and could serve as a biomarker for *CYP3A4* metabolizer phenotype. The reported allele frequency of *CYP3A4*22* is 5% to 8% in the white population and 4.3% in African American and Chinese populations.

Other alleles have not been as extensively studied in clinical trials but are expected to have similar impacts on statin metabolism and the metabolism of other drugs primarily metabolized by CYP3A4.

The following table displays the *CYP3A4* variants detected by this assay, the corresponding star allele, and the effect on CYP3A4 enzyme activity. Individuals without a detectable *CYP3A4* variant are designated as *CYP3A4*1/*1*.

***CYP3A4* allele**	**cDNA nucleotide change (NM_017460.5)**	**Effect on enzyme activity**
**1*	None (wild type)	Normal activity
**8*	c.389G>A	No activity
**11*	c.1088C>T	Reduced activity
**12*	c.1117C>T	Reduced activity
**13*	c.1247C>T	No activity
**16*	c.554C>G	Minimal activity
**17*	c.566T>C	No activity
**18*	c.878T>C	Reduced activity

*22	c.522-191C>T	Reduced activity
*26	c.802C>T	No activity

Genotype to phenotype predictions are based on the Pharmacogene Variation Consortium website (3) and review of the *CYP3A4* literature.

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(3)

For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Cautions

Rare variants may be present that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing could be considered.

Samples may contain donor DNA if obtained from patients who received non-leukoreduced blood transfusions or allogeneic hematopoietic stem cell transplantation. Results from samples obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic hematopoietic stem cell transplantation, a pretransplant DNA specimen is recommended for testing.

CYP3A4 genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's CYP3A4 status.

This test does not detect all variants that result in altered CYP3A4 activity. Therefore, absence of a detectable variant does not rule out the possibility that a patient has altered CYP3A4 metabolism due to other *CYP3A4* variants that cannot be detected with this method. Furthermore, when 2 or more variants are identified, the cis-/trans- status (whether the variants are on the same or opposite chromosomes) is not always known.

Drug-drug interactions and drug-metabolite inhibition must be considered.

Drug-metabolite inhibition can occur, resulting in inhibition of CYP3A4 catalytic activity.

Patients may also develop toxicity problems if liver and kidney function are impaired.

Clinical Reference

1. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science. 1999;286(5439):487-491. doi: 10.1126/science.286.5439.487

2. Wang D, Guo Y, Wrighton SA, Cooke GE, Sadee W. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. Pharmacogenomics J. 2011;11(4):274-286. doi:10.1038/tpj.2010.28
3. PharmVar: Pharmacogene Variation Consortium. Updated March 3, 2021. Accessed March 22, 2021. Available at www.pharmvar.org/
4. Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev. 2002;54(10):1271-1294. doi: 10.1016/s0169-409x(02)00066-2
5. Elens L, Becker ML, Haufroid V, et al. Novel CYP3A4 intron 6 single nucleotide polymorphism is associated with simvastatin-mediated cholesterol reduction in the Rotterdam Study. Pharmacogenet Genomics. 2011;21(12):861-866. doi: 10.1097/FPC.0b013e32834c6edb
6. Elens L, van Schaik RH, Panin N, et al. Effect of a new functional CYP3A4 polymorphism on calcineurin inhibitors' dose requirements and trough blood levels in stable renal transplant patients. Pharmacogenomics. 2011;12(10):1383-1396. doi: 10.2217/pgs.11.90
7. Clinical Pharmacogenetics Implementation Consortium (CPIC). Accessed October 14, 2020. https://cpicpgx.org/

Performance

Method Description
Genomic DNA is extracted from whole blood or saliva. Genotyping for the *CYP3A4* alleles is performed using a polymerase chain reaction (PCR)-based 5'-nuclease assay. Fluorescently labeled detection probes anneal to the target DNA. PCR is used to amplify the section of DNA that contains the variant. If the detection probe is an exact match to the target DNA, the 5'-nuclease polymerase degrades the probe, the reporter dye is released from the effects of the quencher dye, and a fluorescent signal is detected. Genotypes are assigned based on the allele-specific fluorescent signals that are detected.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
3 to 8 days

Specimen Retention Time
Whole Blood/Saliva Swab: 2 weeks; Extracted DNA: 2 months

Performing Laboratory Location
Rochester

Fees & Codes

Fees

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

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

81230-CYP3A4

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
3A4Q	CYP3A4 Genotype, V	74007-6

Result ID	Test Result Name	Result LOINC® Value
610110	CYP3A4 Genotype	81139-8
610111	CYP3A4 Phenotype	81145-5
610112	Interpretation	69047-9
610113	Additional Information	48767-8
610114	Method	85069-3
610115	Disclaimer	62364-5
610116	Reviewed by	18771-6