

Angioedema and Complement Disorders Gene Panel, Varies

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inherited complement disorder, including complement deficiency

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary angioedema, including those with absent or dysfunctional C1-inhibitor protein

Establishing a diagnosis of a complement disorder or hereditary angioedema, allowing for appropriate management and surveillance for disease features based on the gene or variant involved

Identifying variants within genes known to be associated with complement disorders and hereditary angioedema, allowing for predictive testing of at-risk family members

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULAF	Amniotic Fluid	Yes	No
	Culture/Genetic Test		
_STR1	Comp Analysis using STR	No, (Bill only)	No
	(Bill only)		
_STR2	Add'l comp analysis w/STR	No, (Bill only)	No
	(Bill Only)		
CULFB	Fibroblast Culture for	Yes	No
	Genetic Test		
MATCC	Maternal Cell	Yes	No
	Contamination, B		

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 28 genes associated with a complement component deficiency or hereditary angioedema: *ANGPT1, C1QA, C1QB, C1QC, C1R, C1S, C2, C3, C5, C6, C7, C8A, C8B, C9, CD46, CD55, CD59, CFB, CFD, CFH, CFI, CFP, F12, KNG1, MASP2, PLG, SERPING1,* and *THBD*. See <u>Targeted Genes and Methodology Details for Angioedema and Complement Disorders Gene Panel</u> and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for complement component deficiencies or hereditary angioedema.

Testing Algorithm

Skin biopsy:



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For skin biopsy or cultured fibroblast specimens, a fibroblast culture will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Cord blood:

For cord blood specimens that have an accompanying maternal blood specimen, maternal cell contamination studies will be performed at an additional charge.

Special Instructions

- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- <u>Blood Spot Collection Instructions</u>
- <u>Complement Component Deficiency and Hereditary Angioedema Patient Information</u>

Method Name

Sequence Capture and Amplicon-Based Next-Generation Sequencing (NGS) followed by Droplet Digital Polymerase Chain Reaction (ddPCR)/Quantitative Real-Time Polymerase Chain Reaction (qPCR) and Sanger Sequencing as needed

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Patients who have had a previous bone marrow transplant from an allogenic donor should not have testing performed on blood, bone marrow, or saliva because any results generated will reflect the genome of the donor rather than the recipient. Testing on patients who have an active hematologic malignancy or hematologic disorder with clonal proliferation may identify both somatic mutations and germline variants, which may result in test failure or necessitate follow-up testing to determine whether the detected variant is germline or somatic. For these patients, testing a skin biopsy or cultured fibroblasts is recommended. For instructions for testing patients who have received a bone marrow transplant or have an active hematologic disorder, call 800-533-1710. For more information see Cautions.

For patients with hereditary angioedema with normal C1 inhibitor, see GNANG / Hereditary Angioedema Focused Gene Panel, Next-Generation Sequencing, Varies for a smaller panel that includes *F12*, *KNG1*, and *PLG*.

For patients suspected to have complement C3 glomerulopathy or a complement-mediated thrombotic microangiopathy, also known as atypical hemolytic uremic syndrome, a different test is recommended. Order AHUGP / Atypical Hemolytic Uremic Syndrome (aHUS)/Thrombotic Microangiopathy (TMA)/Complement 3 Glomerulopathy (C3G)



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Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies. To modify this panel via CGPH, use the Inborn Errors of Immunity/Bone Marrow Failure/Telomeropathy/Pulmonary Fibrosis/Very Early Onset IBD/Pancreatitis disease state for step 1 on the <u>Custom Gene Ordering Tool</u>.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Additional Testing Requirements

For cord blood specimens: Maternal cell contamination (MCC) studies are available. **Order MATCC /** Maternal Cell Contamination, Molecular Analysis, Varies **on both the cord blood and maternal specimens under separate order numbers**. Cord blood testing will proceed without MCC studies, but results may be compromised if MCC is present.

Specimen Required

Patient Preparation: A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Specimen Type: Whole blood Container/Tube: Preferred: Lavender top (EDTA) or yellow top (ACD) Acceptable: Green top (Sodium heparin) Specimen Volume: 3 mL **Collection Instructions:** 1. Invert several times to mix blood. 2. Send whole blood specimen in original tube. Do not aliquot. Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days Additional Information: 1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed. 2. To ensure minimum volume and concentration of DNA is met, the required volume must be submitted. Testing may be canceled if DNA requirements are inadequate. Specimen Type: Skin biopsy Supplies: Fibroblast Biopsy Transport Media (T115) Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.

Specimen Volume: 4-mm Punch

Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours Additional Information:



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1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.

2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblasts

Source: Skin

Container/Tube: T-25 flask

Specimen Volume: 2 Flasks

Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy. Cultured cells from a prenatal specimen will not be accepted.

Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours

Additional Information:

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.

2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical and Molecular Testing, Tissue. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

Specimen Type: Extracted DNA

Container/Tube:

Preferred: Screw Cap Micro Tube, 2 mL with skirted conical base

Acceptable: Matrix tube, 1 mL

Collection Instructions:

1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.

2. Include concentration and volume on tube.

Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated

Additional Information: DNA must be extracted in a CLIA-certified laboratory, or equivalent, and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

Specimen Type: Bone marrow aspirate
Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Yellow top (ACD)
Specimen Volume: 2 mL
Collection Instructions:

Invert several times to mix bone marrow.
Label specimen as bone marrow.
Send bone marrow specimen in original tube. Do not aliquot.

Specimen Stability Information: Ambient 4 days/Refrigerated 4 days/Frozen 4 days

Additional Information:



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1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.

2. To ensure minimum volume and concentration of DNA is met, the required volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Cord blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Green top (sodium heparin)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send cord blood specimen in original tube. **Do not aliquot**.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days

Additional Information:

1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.

2. To ensure minimum volume and concentration of DNA is met, the required volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

3. While a properly collected cord blood sample may not be at risk for maternal cell contamination, unanticipated complications may occur during collection. Therefore, maternal cell contamination studies are recommended to ensure the test results reflect that of the patient tested and are available at an additional charge. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Specimen Type: Blood spot

Supplies: Card-Blood Spot Collection (Filter Paper) (T493)

Container/Tube:

Preferred: Collection card (Whatman Protein Saver 903 Paper)

Acceptable: PerkinElmer 226 filter paper or blood spot collection card

Specimen Volume: 2 to 5 Blood spots

Collection Instructions:

1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see <u>How to Collect a Dried Blood Spot Sample</u>.

2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.

- 3. Do not expose specimen to heat or direct sunlight.
- 4. Do not stack wet specimens.

5. Keep specimen dry.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Additional Information:

1. Blood spot specimens are acceptable but not recommended. Multiple extractions will be required to obtain sufficient yield for supplemental analysis, and there is significant risk for test failure due to insufficient DNA.

2. Due to lower concentration of DNA yielded from blood spot, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.



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3. For collection instructions, see **Blood Spot Collection Instructions**

- 4. For collection instructions in Spanish, see <u>Blood Spot Collection Card-Spanish Instructions</u> (T777)
- 5. For collection instructions in Chinese, see <u>Blood Spot Collection Card-Chinese Instructions</u> (T800)

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: 2 Swabs, use 2 kits for collection

Collection Instructions: Collect and send specimen per kit instructions.

Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days

Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

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:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing (Spanish) (T826)

2. Complement Component Deficiency and Hereditary Angioedema Patient Information

Specimen Minimum Volume

See Specimen Required

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

The complement system is an essential component of the innate immune system, which is present from birth and is responsible for immune mediation and responding to pathogens. Deficiency or dysregulation of the complement system can result in a wide spectrum of clinical presentations depending on the specific component that is impacted. Many complement disorders are due to loss-of-function variants that result in recurrent or chronic bacterial infections and autoimmunity due to complement deficiencies. These disorders are mostly inherited in an autosomal recessive pattern. Deficiency of complement regulators may result in complement dysregulation (also known as primary immune regulatory disorder: PIRD) such as complement-mediated thrombotic microangiopathy (CM-TMA). For these disorders,



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order a different gene panel, AHUGP / Atypical Hemolytic Uremic Syndrome (aHUS)/Thrombotic Microangiopathy (TMA) /Complement 3 Glomerulopathy (C3G) Gene Panel, Varies. This gene panel is focused on complement component deficiencies.

Early classical complement deficiencies (eg, C1, C2) typically present with susceptibility to encapsulated bacteria, such as *Streptococcus pneumoniae* or *Haemophilus influenza* type b, while C3 deficiency is associated with gram-negative bacteria including *Neisseria meningitidis, Enterobacter aerogenes,* and *Escherichia coli*. Individuals with deficiency of the late common pathway (eg, C5, C6, C7, C8, C9) or deficiency of complement factors D and B in the alternative complement pathway have increased susceptibility to bacterial infections, particularly *Neisseria* infections. In addition, patients with deficiency of the early classical components are at increased risk of autoimmune disorders, including systemic lupus erythematosus (SLE). In some individuals, deleterious variants in genes encoding complement inhibitors, such as *CFH* or *CD46*, may also be at increased risk of SLE and lupus nephritis. Individuals with C3 deficiency may also develop mesangiocapillary or membranoproliferative glomerulonephritis and kidney failure.

Cluster of differentiation 55 (CD55), or complement decay-accelerating factor (DAF), is a cell surface complement regulator. CD55 deficiency is characterized by hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy, and is also known as CHAPLE syndrome. This is also an autosomal recessive disorder. For diseases with mainly gastrointestinal presentations, order EOIBD / Early Onset Monogenic Inflammatory Bowel Disease (IBD) Gene Panel, Varies. For diseases with mainly autoinflammatory presentations, order AUTOG / Autoinflammatory Disorders Gene Panel, Varies.

Hereditary angioedema (HAE) is typically inherited in an autosomal dominant pattern and characterized by recurrent episodes of severe swelling of the upper airways, skin, or gastrointestinal tract. These episodes may last from 2 to 5 days and have minimal response to antihistamines, corticosteroids, and epinephrine. HAE is most frequently due to variants in the *SERPING1* gene that encodes the C1-inhibitor (C1-INH). C1-INH functions in complement inhibition to prevent spontaneous activation but is also important in inhibition of proteases involved in the fibrinolytic, clotting, and kinin pathways. A subset of individuals with HAE has normal C1-INH, which is associated with variants in *F12, KNG1, PLG*, and *ANGPT1*. For a panel targeted to HAE with normal C1-INH, order GNANG / Hereditary Angioedema Focused Gene Panel, Next-Generation Sequencing, Varies.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of



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at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:

Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:

This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic mutations and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For the most up to date list of genes included in this test and detailed information regarding gene-specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukocyte-reduced blood transfusion, results of tests performed on blood, bone marrow, or saliva specimens may be clinically inaccurate due to the presence of donor DNA. Test orders for blood, bone marrow, or saliva will be canceled by the laboratory if there is a history of an allogeneic hematopoietic stem cell transplant. Similarly, blood, bone marrow, and saliva results may be impacted by presence of active hematologic malignancy or hematologic disorder with clonal proliferation. Call Mayo Clinic Laboratories for instructions for testing a skin biopsy or fibroblast culture for patients who have received a bone marrow transplant or have an active hematologic disorder.

Reclassification of Variants:

Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare professionals to contact the laboratory at any time to learn how the



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classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:

Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

2. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3

3. Mollah F, Tam S. Complement deficiency. In: StatPearls [Internet]. StatPearls Publishing; 2024. Updated March 13, 2023. Accessed March 28, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK557581/

4. Costa-Reis P, Sullivan KE. Monogenic lupus: it's all new!. Curr Opin Immunol. 2017;49:87-95

5. Ozen A, Comrie WA, Ardy RC, et al. CD55 deficiency, early-onset protein-losing enteropathy, and thrombosis. N Engl J Med. 2017;377(1):52-61

6. Santacroce R, D'Andrea G, Maffione AB, Margaglione M, d'Apolito M. The genetics of hereditary angioedema: A review. J Clin Med. 2021;10(9):2023. Published 2021 May 9. doi:10.3390/jcm10092023

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions/insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp



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and insertions up to 47 bp. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed. A supplemental droplet digital PCR method is used to detect deletions and duplications in *C1R*.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See <u>Targeted Genes and Methodology Details for Angioedema and Complement Disorders Gene</u> <u>Panel</u> for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Genes analyzed: ANGPT1, C1QA, C1QB, C1QC, C1R, C1S, C2, C3, C5, C6, C7, C8A, C8B, C9, CD46, CD55, CD59, CFB, CFD, CFH, CFI, CFP, F12, KNG1, MASP2, PLG, SERPING1, and THBD

PDF Report Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

Whole blood: 28 days (if available); Saliva: 30 days (if available); Extracted DNA: 3 months; Blood spots: 1 year (if available)

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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 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

81479



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LOINC[®] Information

Test ID	Test Order Name	Order LOINC [®] Value
AECDP	Angioedema and Complement	105329-7
	GenePanel	
	-	
Result ID	Test Result Name	Result LOINC [®] Value
621548	Test Description	62364-5
621549	Specimen	31208-2
621550	Source	31208-2
621551	Result Summary	50397-9
621552	Result	82939-0
621553	Interpretation	69047-9
621554	Additional Results	82939-0
621555	Resources	99622-3
621556	Additional Information	48767-8
621557	Method	85069-3
621558	Genes Analyzed	82939-0
621559	Disclaimer	62364-5
621560	Released By	18771-6
MG151	Is this Bone Marrow	31208-2