MOLECULAR TESTING FOR CHARCOT-MARIE-TOOTH DISORDER

PMP22
CX32
MFN2
MPZ
EGR2
LITAF
PRX
GDAP1
RAB7
GARS
NFL
HSPB1
LMNA
FIG4
SH3TC2
DNM2
YARS
FGD4
NDRG1
TRPV4
HSPB8
MTMR2
SBF2

More than Measurement.
Meaningful Interpretation.

New Tests Available

athena diagnostics®

Testing that Makes a Difference.

Molecular testing services for

Charcot-Marie-Tooth Disorder

Charcot-Marie-Tooth (CMT) is one of the most common, nerve-related, hereditary disorders. It affects approximately 2.6 million people worldwide.[1] There is no cure; however, treatments can include orthopedic surgery, physical therapy, occupational therapy and orthopedic devices.

An accurate diagnosis can help avoid medications that may exacerbate CMT.

Only Athena Diagnostics® offers an algorithmic approach to simplify testing and provide the most efficient path to an accurate diagnosis.

Understanding CMT and its Challenges

Charcot-Marie-Tooth (CMT) disorder, a group of hereditary, progressive peripheral nerve disorders, impairs movement and sensation in a patient's feet and lower legs. Gene mutations prevent transmission of the brain signals to nerves that serve the legs, feet, hands, and arms.

Categorized in four primary groups—1, 2, 4, and X—CMT usually becomes symptomatic in adolescence to early childhood, however onset can occur earlier or later. ***Some carriers may never show signs.***

Depending on the type of CMT, patients may present with:

- Hand atrophy, leg, ankle, or feet weakness
- Loss of muscle bulk in legs and feet
- Foot deformities, such as high arch, hammertoes, footdrop
- Numbness in legs and feet
- Diminished sensation to touch, heat and cold in legs and feet
- Aching or burning sensations in feet and lower legs
- Higher than normal gait
- Frequent tripping or falling

Only Genetic Testing Can Confirm a CMT Differential Diagnosis

CMT is difficult to diagnose clinically, because the condition's type, symptoms, and onset vary widely—and knowing which type of CMT a patient has can make a difference. As many as one-third of patients have no confirmed family history. ***Some people may never show symptoms, or merely overlook mild signs, like hand or foot numbness.***

The only way to confirm the type of CMT is through genetic testing. With this knowledge, you can provide early intervention and appropriate treatments according to type, as well as genetic counseling and prenatal testing for risk assessment.

Syndrome Type	Symptoms	Inheritance	Gene
Type 1	Progressive distal muscle weakness and atrophy and sensory loss, particularly in the lower legs, feet, hands, and forearms, peroneal gait, areflexia, cranial nerve involvement, progressive scoliosis, delayed motor development[2]	AD	*PMP22, MPZ, LITAF, EGR2, NEFL*
Type 2	Sensory loss, feet ulcerations, distal motor weakness, hyperkeratosis, diaphragmal and vocal cord paresis, small hand muscles atrophy, slowly progressive walking difficulties, preserved knee jerks, absent triceps surae jerks, scoliosis, Adie pupils, death (Type 2C)[2]	AD	*MFN2, K1F1B, RAB7A, LMNA, MED25, TRPV4, GARS, NEFL, HSPB1, MPZ, GDAP1, HSPB8, AARS, DYNC1H1, LRSAM1*
Type 2A	Severe early onset, hearing loss, CNS and pyramidal tract involvement[2]	AD	*MFN2* sequence variants, *K1F1B* sequence variants
Type 2E/1F	Onset in early childhood, delayed motor development, severe CMT1 phenotype, similar to DSS, sensory loss of all modalities[2]	AD; AR in rare cases	*NEFL*
Type 4	Severe distal muscle weakness, prominent sensory loss (frequently in Roma population), delay in motor development, coordination disorder, scoliosis, cranial nerves affection, blindness, glaucoma, severe disability, deafness, tongue atrophy (Roma population), generalized hypotonia, arthrogryposis, curvilinear inclusions in nerves, severe distal muscle weakness[2]	AR	*GDAP1, MTMR2, SBF2, SH3TC2, NDRG1, EGR2, PRX, FGD4, FIG4*
Type 4A	Early onset, severe motor retardation, progressive scoliosis[2]	AR	*GDAP1*
Type 4C	Early onset, severe motor retardation, scoliosis, respiratory insufficiency[3]	AR	*SH3TC2*
X Type 1	Moderate to severe motor and sensory neuropathy in males; sensorineural deafness; females present mild or no symptoms if they inherit one mutated gene from one parent and a normal gene from the other, hand/thenar muscles, CNS involvement, visual impairment, white matter lesion[2]	X-Linked Dominant	*GJB1*
X Type 5	Hearing loss, optic neuropathy, females unaffected[2]	X-Linked Dominant	*PRPS1*

Why Testing For CMT Makes A Difference

Only a Genetic Test Can Accurately Diagnose the CMT Subtype. In Addition, Testing may:

Clarify inheritance patterns

- A positive molecular genetic test provides specific information about the inheritance pattern of CMT within a family, which is useful in evaluating risk in family members.
- A negative result excludes the common forms of CMT and will help narrow your search for the true cause.

A molecular diagnosis may help patients avoid contra-indicated medications

- Avoid drug-induced exacerbation of CMT.
- Help educate other clinicians about the risks of medications.

A positive molecular genetic test result may help guide patients toward effective therapeutic strategies.

- Physical Therapy and Exercise
- Assistive Devices
- Pharmacological Symptom Management
- Surgical Intervention

Weimer *et al.* compiled a list of contra-indicated medications segregated into probable relative risk to CMT patients.[4]

Medications that Exacerbate Neuropathy[4]

Definite high risk (including asymptomatic CMT)
Vinca alkaloids (vincristine)

Moderate to significant risk
Amiodarone
Bortezomib (velcade)
Cisplatin, carboplatin, oxaliplatin
Colchicine (extended use)
Dapsone
Didanosine (ddI)
Dichloroacetate
Disulfiram
Gold salts
Leflunomide
Linezolid (extended use)
Metronidazole/misonidazole (extended use)
Nitrofurantoin
Nitrous oxide (inhalation abuse or vitamin B12 deficiency)
Perhexiline*
Pyridoxine (high dose)
Stavudine (d4T)
Suramin
Tacrolimus (FK506, ProGraf)
Taxoids (paclitaxel, docetaxel)
Thalidomide
Zalcitabine

Uncertain or minor risk
5-Fluoracil
Adriamycin
Almitrine*
Chloroquine
Cytarabine (high dose)
Cyclosporin A
Ethambutol
Etoposide (VP-16)
Gemcitabine
Griseofulvin
Hexamethylmelamine
Hydralazine
Ifosphamide
Infliximab
Isoniazid
Mefloquine
Penicillamine
Penicillin – high IV doses
Phenytoin
Podophyllin resin
Sertraline (Zoloft)
Statins
Tumor necrosis factor-a
Zimeldine*
a-Interferon

Negligible or doubtful risk
Allopurinol
Amitriptyline
Chloramphenicol
Chlorprothixene
Cimetidine
Clioquinil
Clofibrate
Enalapril
Fluoroquinolones
Gabapentin
Gluthethimide
Lithium
Phenelzine
Propafenone
Sulfonamides
Sulphasalzine

*Not available in the United States.

The Value of Athena Diagnostics Advanced Sequencing Approach

More Than Measurement. Meaningful Interpretation.

Athena Diagnostics now offers advanced sequencing with an algorithmic approach that simplifies testing procedures and provides the most efficient path to an accurate diagnosis. With a single blood draw, the new reflexive CMT evaluations first test for *PMP22* duplications (when appropriate), which are responsible for 40-50 percent of all CMT cases[2], before automatically reflexing to advanced sequencing of phenotypically relevant genes.

This combination of MLPA and advanced sequencing has enabled us to enhance clinical utility, add additional genes to our testing menu, and reduce the cost of testing for your patient. An internal study of CMT samples has shown that our advanced sequencing testing results are in 100 percent concordance with Sanger sequencing, so you can be sure of a reliable result.

Tier Approach Based on Prevalence, Electrodiagnostic Studies and Inheritance.

For a complete testing algorithm, please visit AthenaDiagnostics.com/algorithm.

The Risk of Undiagnosed Hereditary Peripheral Neuropathy

Case Study: The Importance of Testing for CMT

Allison Moore
Founder and President of the Hereditary Neuropathy Foundation

When it came to needing chemotherapy, what Allison Moore didn't know really did hurt her. Moore was a healthy 29-year-old in training for the New York marathon when her doctors discovered a malignant but treatable tumor in her leg. She underwent combination chemotherapy with vincristine, adriamycin, and cytoxan. While her cancer was treated successfully, she developed severe peripheral neuropathy. Peripheral neuropathy is a recognized side effect of several potent chemotherapy agents, including vincristine, and she was assured she would likely improve over time. But she didn't.

What she didn't know at the time was that the chemotherapy had unmasked a previously asymptomatic hereditary neuropathy called Charcot-Marie-Tooth disease (CMT). As months turned into years with no improvement, she began to look for other causes of her symptoms. Finally, she saw a neurologist who recognized the symptoms and the connection to the chemotherapy. "It took me two-and-a-half years to finally get a diagnosis," Ms. Moore says. "It's the biggest disease no one has ever heard of."

CMT, named for its three co-discoverers, is not one but actually many different genetic disorders with similar symptoms. There are multiple clinical types and subtypes, which differ in their underlying gene, the mode of inheritance, and the spectrum of symptoms produced. The most common is duplication of the peripheral myelin protein 22 (*PMP22*) gene, causing overexpression of the protein and myelin abnormalities. It is inherited as an autosomal dominant condition.

Symptoms include weakness, reduced deep tendon reflexes, loss of muscle bulk, and foot deformities, including hammer toes and high arches. "CMT is the most common cause of inherited peripheral neuropathy with a prevalence of 1 in 2,500 people. It is unfortunate that the genetic diagnosis is not considered more frequently because it identifies medications that are potentially toxic to CMT patients." according to Joseph Higgins, MD, FAAN, Medical Director of Neurology for Athena Diagnostics.

Taking a detailed family history can help avoid problems. "Questions about whether there are relatives who use a cane, or braces, have an orthopedic problem with their feet, or have seen a podiatrist should raise the suspicion. **Some medications are hazardous and should be avoided by all CMT patients including those with no symptoms.**" Dr. Higgins said. "It is important to ask questions about hereditary peripheral neuropathies before prescribing such medications." In Ms. Moore's case, there were clues in her family history—her father had peripheral neuropathy—and she herself had high arches and poor reflexes. "My leg never would go up when they tapped my knee," she noted, but neither she nor her family were informed of the possible implications. "We didn't know it was genetic."

When there is a possibility of a history of peripheral neuropathy, or if medications worsen a neuropathy, a referral to a genetic counselor or a neurologist is indicated. In years past, the wide array of potential genetic diagnoses meant that much effort and expense, including electromyography and nerve conduction studies, went into narrowing the diagnosis by CMT type before ordering a genetic test. That is still good medical practice, Dr. Higgins said. "But with the cost of sequencing coming down, it is now easier to screen for the majority of the CMT types all at once." Genetic counseling is still a vital part of the testing protocol, since the hereditary information and the implications of the test results can still be complex.

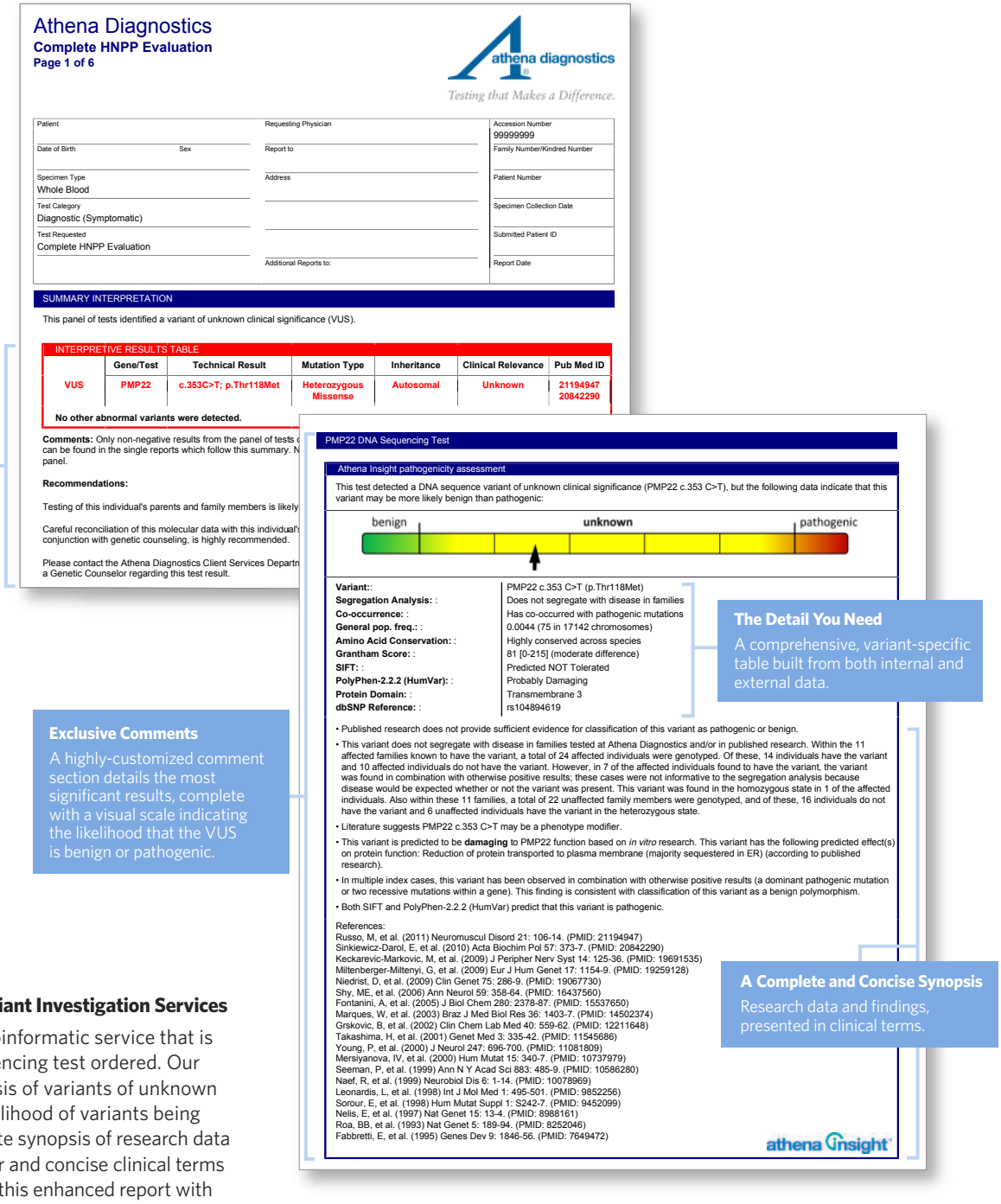
What to do when the patient tests positive for a peripheral neuropathy and still needs chemotherapy? There are important guidelines every oncologist should know. Most significantly, vincristine should never be used in a patient at risk for CMT type 1a, the form due to PMP mutations. This precaution is outlined on a "black box" warning on the drug's prescribing information. There is a long list of other drugs that carry less severe risks, including other chemotherapy agents, antibiotics, and anesthetics. With each, it is important to weigh the risks and benefits for the individual patient in light of their genetic diagnosis. A full discussion and list of drugs of concern can be found at the National CMT Resource Center website, help4cmt.com/factsheets/?t=Neurotoxic Drugs

Ms. Moore can no longer run marathons, but she does ride in bike-a-thons and remains physically active despite her CMT. She is the founder and president of the Hereditary Neuropathy Foundation, and serves as the Consumer Advisor to the National CMT Resource Center. Educating physicians about these unrecognized risks "is one of our missions," she says. "The oncology community needs to know."

In her own words:
Allison Moore discusses her battle with CMT
Visit AthenaDiagnostics.com/NeuroLink

Comprehensive Services from Athena Diagnostics

Athena Insight is a powerful result-reporting service that is included with every DNA sequencing test ordered.



Athena Diagnostics
Complete HNPP Evaluation
Page 1 of 6

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Testing that Makes a Difference.

Patient	Requesting Physician	Accession Number
		99999999
Date of Birth / Sex	Report to	Family Number/Kindred Number
Specimen Type: Whole Blood	Address	Patient Number
Test Category: Diagnostic (Symptomatic)		Specimen Collection Date
Test Requested: Complete HNPP Evaluation		Submitted Patient ID
	Additional Reports to:	Report Date

SUMMARY INTERPRETATION

This panel of tests identified a variant of unknown clinical significance (VUS).

INTERPRETIVE RESULTS TABLE

	Gene/Test	Technical Result	Mutation Type	Inheritance	Clinical Relevance	Pub Med ID
VUS	PMP22	c.353C>T; p.Thr118Met	Heterozygous Missense	Autosomal	Unknown	21194947 20842290

No other abnormal variants were detected.

Comments: Only non-negative results from the panel of tests can be found in the single reports which follow this summary. N panel.

Recommendations:

Testing of this individual's parents and family members is likely

Careful reconciliation of this molecular data with this individual conjunction with genetic counseling, is highly recommended.

Please contact the Athena Diagnostics Client Services Departn a Genetic Counselor regarding this test result.

PMP22 DNA Sequencing Test

Athena Insight pathogenicity assessment

This test detected a DNA sequence variant of unknown clinical significance (PMP22 c.353 C>T), but the following data indicate that this variant may be more likely benign than pathogenic:

benign — unknown — pathogenic

Variant::	PMP22 c.353 C>T (p.Thr118Met)
Segregation Analysis: :	Does not segregate with disease in families
Co-occurrence: :	Has co-occurred with pathogenic mutations
General pop. freq.: :	0.0044 (75 in 17142 chromosomes)
Amino Acid Conservation: :	Highly conserved across species
Grantham Score: :	81 [0-215] (moderate difference)
SIFT: :	Predicted NOT Tolerated
PolyPhen-2.2.2 (HumVar): :	Probably Damaging
Protein Domain: :	Transmembrane 3
dbSNP Reference: :	rs104894619

- Published research does not provide sufficient evidence for classification of this variant as pathogenic or benign.
- This variant does not segregate with disease in families tested at Athena Diagnostics and/or in published research. Within the 11 affected families known to have the variant, a total of 24 affected individuals were genotyped. Of these, 14 individuals have the variant and 10 affected individuals do not have the variant. However, in 7 of the affected individuals found to have the variant, the variant was found in combination with otherwise positive results; these cases were not informative to the segregation analysis because disease would be expected whether or not the variant was present. This variant was found in the homozygous state in 1 of the affected individuals. Also within these 11 families, a total of 22 unaffected family members were genotyped, and of these, 16 individuals do not have the variant and 6 unaffected individuals have the variant in the heterozygous state.
- Literature suggests PMP22 c.353 C>T may be a phenotype modifier.
- This variant is predicted to be **damaging** to PMP22 function based on *in vitro* research. This variant has the following predicted effect(s) on protein function: Reduction of protein transported to plasma membrane (majority sequestered in ER) (according to published research).
- In multiple index cases, this variant has been observed in combination with otherwise positive results (a dominant pathogenic mutation or two recessive mutations within a gene). This finding is consistent with classification of this variant as a benign polymorphism.
- Both SIFT and PolyPhen-2.2.2 (HumVar) predict that this variant is pathogenic.

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athena insight

Interpretation and Results
A clear and concise interpretation field qualifies the Variant of Unknown Significance (VUS) and provides the information at a glance.

Exclusive Comments
A highly-customized comment section details the most significant results, complete with a visual scale indicating the likelihood that the VUS is benign or pathogenic.

The Detail You Need
A comprehensive, variant-specific table built from both internal and external data.

A Complete and Concise Synopsis
Research data and findings, presented in clinical terms.

Athena Insight™ Complete Variant Investigation Services

Athena Insight is a powerful bioinformatic service that is included with every DNA sequencing test ordered. Our technical comprehensive analysis of variants of unknown significance determines the likelihood of variants being benign or pathogenic. A complete synopsis of research data and findings is presented in clear and concise clinical terms enabling the physician to utilize this enhanced report with patients and family members during discussions relative to diagnosis, treatment, patient management and family planning.

Genetic Counselors at Your Service

Genetic Counselors can provide information on the nature, inheritance, and implications of genetic disorders to help the physician guide the patient and family in making informed medical and personal decisions.

References: 1. What is Charcot-Marie-Tooth Disorder (CMT)?, Charcot-Marie-Tooth Association, http://cmtausa.org/index.php?option=com_content&view=article&id=70&Itemid=159
2. Barisic, N., Claeys, K. G., Sirotković -Skerlev, M., Löfgren, A., Nelis, E., De Jonghe, P. and Timmerman, V. (2008), Charcot-Marie-Tooth Disease: A Clinico-genetic Confrontation. *Annals of Human Genetics*, 72: 416–441. 3. Charcot-Marie-Tooth Disease Fact Sheet, *National Institute of Neurological Disorders and Stroke*, April 2007 (NIH Publication No. 07-4897). 4. Weimer, L.H.; Podwall, D., Medication-induced exacerbation of neuropathy in Charcot Marie Tooth Disease. *Journal of the Neurological Sciences*. 242 (2006) 47-54.

Any person depicted in this material is a model with the exception of the case study, Allison Moore, Importance of Testing for CMT.

Comprehensive Test Menu for Charcot-Marie-Tooth Disorder

	Test Code	Test Name	Gene(s) Tested	Specimen Volume (Whole blood)	Turnaround Time
NEW	4001	CMT Advanced Evaluation - Comprehensive	Step 1: *PMP22* Dup./Del. Step 2: *PMP22* Seq., *CX32, MFN2, MPZ, EGR2, LITAF, PRX, GDAP1, RAB7, GARS, NFL, HSPB1, LMNA, FIG4, SH3TC2, DNM2, YARS, FGD4, NDRG1, TRPV4, HSPB8, MTMR2, SBF2*	15 mL Lavender top tube	28 days
NEW	4002	CMT Advanced Evaluation - Dominant, Demyelinating	Step 1: *PMP22* Dup./Del. Step 2: *PMP22* Seq., *MPZ, EGR2, LITAF, DNM2, YARS*	15 mL Lavender top tube	28 days
NEW	4003	CMT Advanced Evaluation - Dominant, Axonal	*MFN2, MPZ, RAB7, GARS, NFL, HSPB1, LMNA, DNM2, YARS, TRPV4, HSPB8*	15 mL Lavender top tube	28 days
NEW	4004	CMT Advanced Evaluation - Recessive, Demyelinating	*PRX, GDAP1, SBF2, SH3TC2, MTMR2, NDRG1, FGD4, FIG4*	15 mL Lavender top tube	28 days
NEW	4005	CMT Advanced Evaluation - Dominant	Step 1: *PMP22* Dup./Del. Step 2: *PMP22* Seq., *MFN2, MPZ, EGR2, LITAF, RAB7, GARS, NFL, HSPB1, DNM2, YARS, TRPV4, HSPB8*	15 mL Lavender top tube	28 days
NEW	4006	CMT Advanced Evaluation – Recessive	*PRX, GDAP1, SBF2, LMNA, FIG4, SH3TC2, MTMR2, NDRG1, FGD4*	15 mL Lavender top tube	28 days
NEW	4007	CMT Advanced Evaluation – Demyelinating	Step 1: *PMP22* Dup./Del. Step 2: *PMP22* Seq., *Cx32, MPZ, EGR2, LITAF, PRX, GDAP1, DNM2, YARS, SH3TC2, MTMR2, NDRG1, FGD4,FIG4, SBF2*	15 mL Lavender top tube	28 days
NEW	4008	CMT Advanced Evaluation – Axonal	*MFN2, Cx32, MPZ, RAB7, GARS, NFL, HSPB1, GDAP1, DNM2, YARS, LMNA, TRPV4, HSPB8*	15 mL Lavender top tube	28 days
NEW	253	DNM2 DNA Sequencing Test	*DNM2* Sequencing	10 mL Lavender top tube	28 days
NEW	468	YARS DNA Sequencing Test	*YARS* Sequencing	10 mL Lavender top tube	28 days
NEW	208	FGD4 DNA Sequencing Test	*FGD4* Sequencing	10 mL Lavender top tube	28 days
NEW	394	NDRG1 DNA Sequencing Test	*NDRG1* Sequencing	10 mL Lavender top tube	28 days
NEW	144	TRPV4 DNA Sequencing Test	*TRPV4* Sequencing	10 mL Lavender top tube	28 days
NEW	463	HSPB8 DNA Sequencing Test	*HSPB8* Sequencing	10 mL Lavender top tube	28 days
NEW	354	MTMR2 DNA Sequencing Test	*MTMR2* Sequencing	10 mL Lavender top tube	28 days
NEW	164	SBF2 DNA Sequencing Test	*SBF2* Sequencing	10 mL Lavender top tube	28 days
	221	GDAP1 DNA Sequencing Test	*GDAP1* Sequencing	10 mL Lavender top tube	28 days
	222	LITAF/SIMPLE DNA Sequencing Test	*LITAF/SIMPLE* Sequencing	10 mL Lavender top tube	28 days
	223	MFN2 DNA Sequencing Test	*MFN2* Sequencing	10 mL Lavender top tube	28 days
	239	Periaxin DNA Sequencing Test	*Periazin* Sequencing	10 mL Lavender top tube	28 days
	247	PMP22 DNA Sequencing Test	*PMP22* Sequencing	10 mL Lavender top tube	28 days
	131	PMP22 Duplication/Deletion Test	*PMP22* Duplication/Deletion	10 mL Lavender top tube	28 days
	248	EGR2 DNA Sequencing Test	*EGR2* Sequencing	10 mL Lavender top tube	28 days
	249	NFL DNA Sequencing Test	*NFL* Sequencing	10 mL Lavender top tube	28 days
	134	MPZ DNA Sequencing Test	*MPZ* Sequencing	10 mL Lavender top tube	28 days
	226	LMNA DNA Sequencing Test	*LMNA* Sequencing	10 mL Lavender top tube	28 days
	224	SH3TC2 DNA Sequencing Test	*SH3TC2* Sequencing	10 mL Lavender top tube	28 days
	227	RAB7 DNA Sequencing Test	*RAB7* Sequencing	10 mL Lavender top tube	28 days
	225	FIG4 DNA Sequencing Test	*FIG4* Sequencing	10 mL Lavender top tube	28 days
	228	GARS DNA Sequencing Test	*GARS* Sequencing	10 mL Lavender top tube	28 days
	143	Connexin32 Evaluation	*Connexin32* Sequencing/Deletion	10 mL Lavender top tube	28 days
	229	HSPB1 DNA Sequencing Test	*HSPB1* Sequencing	10 mL Lavender top tube	28 days

Client Services Representatives are available from 8:30am to 6:30pm Eastern Time (U.S.). Customers in the U.S. and Canada please call toll free **800-394-4493** or visit us on our website at **AthenaDiagnostics.com.**

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Testing that Makes a Difference.

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