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2021 4th edition

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NMO and Anti-aquaporin-4 IgG Antibody Test

(Anti-Aquaporin-4 IgG Antibody)

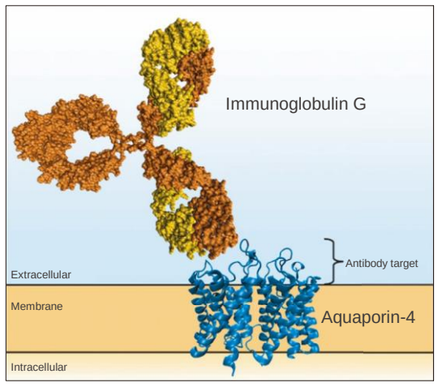
Department of Laboratory Medicine
Jiwon Lee MD

Diagnosis of NMO

Neuromyelitis optica (NMO) is an inflammatory demyelinating autoimmune disease that repeatedly invades the central nervous system: the brain, the optic nerves, or the spinal cord. There are two inflammatory demyelinating diseases that affect the central nervous system: NMO and multiple sclerosis (MS). NMO had long been known as one of the sub-types of MS, until an autoantibody specific to NMO (anti-aquaporin-4, or anti-AQP-4) was found in the serum of an NMO patient in 2004. The discovery proved that NMO is different from MS.

In NMO, the anti-AQP-4 autoantibody destroys the astrocyte and the blood brain barrier (BBB) whereas, in MS, T-lymphoids generated by molecular mimicry work as autoantibodies, and damage the myelogeny of the spinal fluid after passing the BBB. The differential diagnosis of NMO and MS are commonly experienced by clinicians, and the diagnosis can be facilitated by clinical symptoms and imaging findings specific to NMO and anti-AQP-4 antibody tests.

The anti-AQP-4 antibody currently plays a crucial role in NMO diagnosis. The antibody is found in 75% of NMO patients. An anti-AQP-4 antibody test using the cell-based assay (CBA) method is known to show 90% or higher sensitivity and specificity close to 100% for recurrent NMO patients.



Ref) Clinical and Experimental Neuroimmunology 5 (2014) 290–303

Fig. 1. Assays are developed to detect the interaction of immunoglobulin G with aquaporin-4.

Previous diagnostic criteria for NMO included the inflammation of the optic nerves or the spinal cord. However, to account for the possibility of more limited or widespread invasion of the central nervous system, in 2015, the International Panel for NMO Diagnosis (IPND) announced new diagnostic criteria for the NMO spectrum disorders (NMOSD).

The NMOSD refers to NMO-related diseases and other diseases with positive anti-AQP-4 antibodies including: longitudinally extensive transverse myelitis (LETM); recurrent isolated optic neuritis (RION); bilateral optic neuritis (BON); anti-AQP-4-positive diseases with coexisting autoimmune disorders; anti-AQP-4 antibody-positive optic neuritis, myelitis; or optic neuritis or myelitis with typical brain lesions in NMO patients.

Table 1. Diagnostic criteria for Neuromyelitis Optica Spectrum Syndrome (NMOSD)

Diagnostic criteria for NMOSD with AQP4-IgG
1. at least 1 core clinical characteristic 2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) 3. Exclusion of alternative diagnoses
Core clinical characteristics
1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Ref) Neurology 2015;85:177-189

Anti-aquaporin-4 IgG Antibody Test

There are numerous techniques to detect anti-AQP-4 antibodies which include: the indirect immunofluorescence (IIF); the cell-based assay (CBA); the fluoroimmunoprecipitation assay (FIPA); the radioimmunoprecipitation assay (RIPA), and the enzyme-linked immunosorbent assay (ELISA).

The tissue-based IIF is the first immunology test developed for NMO diagnosis. It involves adding in diluted serum to mouse brain tissues and washing it, then using goat anti-human IgG with flueorescein as a secondary antibody to observe the sample with fluorescent microscopes. When testing with anti-AQP-4 antibody-positive serum, the pial surface and the space around blood vessels (Virchow-Robin space) are stained with fluorescent. In the CBA, human embryonic kidney cells (HEK cells) transfected with human AQP-4 are injected with goat anti-human IgG with fluorescein, to observe whether fluorescence manifests on the cell surface (Fig. 2).

Anti-AQP-4 antibody tests are typically performed with serum. Despite some controversy over the efficacy of an additional test using the cerebrospinal fluid for a patient who tested negative in a serum specimen, many experts recommend an additional cerebrospinal fluid test for patients with strongly suspected NMO with negative result for the serological anti-AQP-4 antibody.

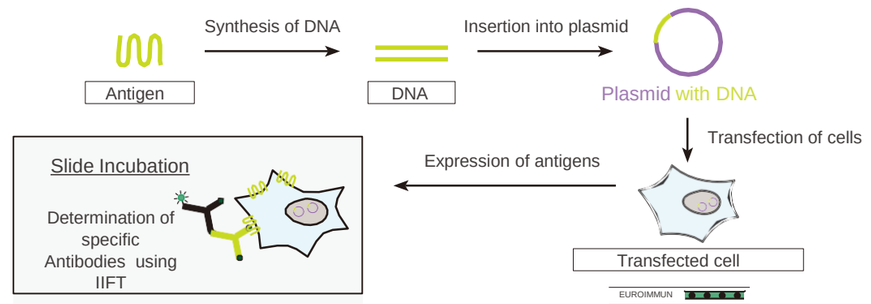


Fig. 2. Recombinant cell-based indirect immunofluorescence assay

Test Considerations

In anti-AQP-4 antibody tests, a positive result is definitive proof of NMO, whereas a negative result does not completely rule out the disease. The immunofluorescence assay is known to show lower sensitivity than the flow cytometry especially in low-titer specimen. Caution is required when interpreting the test results, and confirmatory diagnosis of the disease requires a comprehensive consideration of test results and clinical manifestations.

Test Items Guide

Test Items	Specimen (mL)	Test date/time requirement	Test method	Insurance information
Anti-Aquaporin 4 IgG Antibody (GC Labs code: K023)	Serum 2.0	Mon, Thu / 1 day	IFA	Nu 810 Ga / D810100C

* The above information is as of October 1, 2021, and may change later. Please visit our website for the latest updates (http://www.gclabs.co.kr).

Testing Information

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References

1. Namhee Kim, "Differential Diagnosis between Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder," *Journal of Korean Neurol Association*, 2016; 34:290-6.
2. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89.
3. Waters PJ, McKeon A, Leite MI, Rajasekharan S, Lennon VA, Villalobos A, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. Neurology 2012;78:665-71.
4. Waters P and Vincent A. Detection of anti-aquaporin-4 antibodies in neuromyelitis optica: current status of the assays. The International MS Journal 2008;15:99-106.
5. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. The Lancet 2004;364:2106-12.
6. Waters PJ, Pittock SJ, Bennett JL, Jarius S, Weinshenker BG, Wingerchuk DM, et al. Evaluation of aquaporin-4 antibody assays. Clinical and Experimental Neuroimmunology 2014;5:290-303.

Peroxisomal Disorders, Serological Markers, and Phytanic Acid and Pristanic Acid

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Structure and Functions of Peroxisome

The peroxisome is a pocket-shaped subcellular organelle. It contains around 60 known enzymes required to decompose various materials. The peroxisome is found in all cells, but exists in highest concentrations in the liver and the kidneys. Mature red blood cells do not have a peroxisome. However, the peroxisome exists when membranes are formed in the early stages of red blood cell development.

The currently known key functions of the peroxisome include:

(1) the breakdown of hydrogen peroxide via catalase, among other functions

(2) the ß-oxidation of a range of fatty acids and fatty acid derivatives including very-long-chain fatty acids (VLCFAs) and pristanic acids

(3) the biosynthesis of a special group of phospholipids (plasmalogen) called ether phospholipid, which is a key component of the cellular membrane and the myelin.

(4) the α-oxidation of 3-methyl-branched fatty acids like phytanic acid

(5) the detoxification of glyoxylate via the peroxisomal enzyme alanine glyoxylate aminotransferase (AGT)

(6) the oxidation of L-pipecolic acid, a metabolite of L-lysine, via L-pipecolate oxidase

(7) the oxidation of glutaryl-CoA via glutaryl-CoA oxidase

(8) fatty acid chain elongation

(9) Synthesis of bile acids and cholesterol

Classification and Incidence Rates of the Peroxisomal Disorders

Peroxisomal disorders are diseases associated with peroxisome dysfunction. They manifest a wide range of genetic characteristics. They are categorized into two groups: peroxisome biogenesis disorders (PBDs) caused by defects in the genes(*PEX*) that code peroxin required for the biosynthesis of peroxisome; and peroxisomal disorders caused by the deficiency of a single peroxisome-related enzyme without any defect in the peroxisomal structure.

Table 1. Classification of the peroxisomal disorders

Peroxisome biogenesis disorders (PBDs)	Single peroxisomal enzyme deficiencies
Zellweger spectrum disorders (ZSD)	X-linked adrenoleukodystrophy/adrenomyeloneuropathy (X-ALD/AMN)
Zellweger syndrome (ZWS) (Severe ZSD)	Refsum disease (Classic, Adult) (phytanoyl CoA hydroxylase deficiency)
Neonatal adrenoleukodystrophy (NALD) (Intermediate/milder ZSD)	Acyl CoA oxidase deficiency (pseudo-NALD)
Infantile Refsum disease (IRD) (Intermediate/milder ZSD)	D-bifunctional protein deficiency (DBP deficiency)
Rhizomelic chondrodysplasia punctata type 1 (RCDP1)	Rhizomelic chondrodysplasia punctata type 2 (RCDP2; dihydroxy-acetone phosphate acyltransferase deficiency)
	Rhizomelic chondrodysplasia punctata type 3 (RCDP3; alkyldihydroxyacetone phosphate synthase deficiency)
	Alpha-methylacyl-CoA racemase (AMACR) deficiency
	Peroxisomal sterol carrier protein-X deficiency (SCPx deficiency)
	Acatalasemia
	Hyperoxaluria type 1 (alanine glyoxylate aminotransferase deficiency)

Ref) www.uptodate.com, www.ncbi.nlm.nih.gov/books/NBK1448

In case of Zellweger spectrum disorders, three diseases are considered to represent a clinical continuum. The Zellweger syndrome is the most severe, and the infantile Refsum disease (IRD) is considered the mildest. The neonatal adrenoleukodystrophy (NALD) is known to be a moderate disease. In recent years, the three diseases have been called severe/moderate/mild ZSD, respectively.

In case of RCDP1, despite the existence of peroxisome, mutation in the *PEX7* gene causes deficiency in a specific group of proteins. It damages two peroxisome functions: synthesis of etherphospholipids and alpha-oxidation of phytanic acid.

Peroxisomal disorders are estimated to be contracted by 1 to 5 in every 10,000 newborns. In a study, peroxisomal disorders were found in 2.7% of the 1,000 patients with inborn errors of metabolism diagnosed at Necker–Enfants Malades, Paris, France between 1982 and 1997.

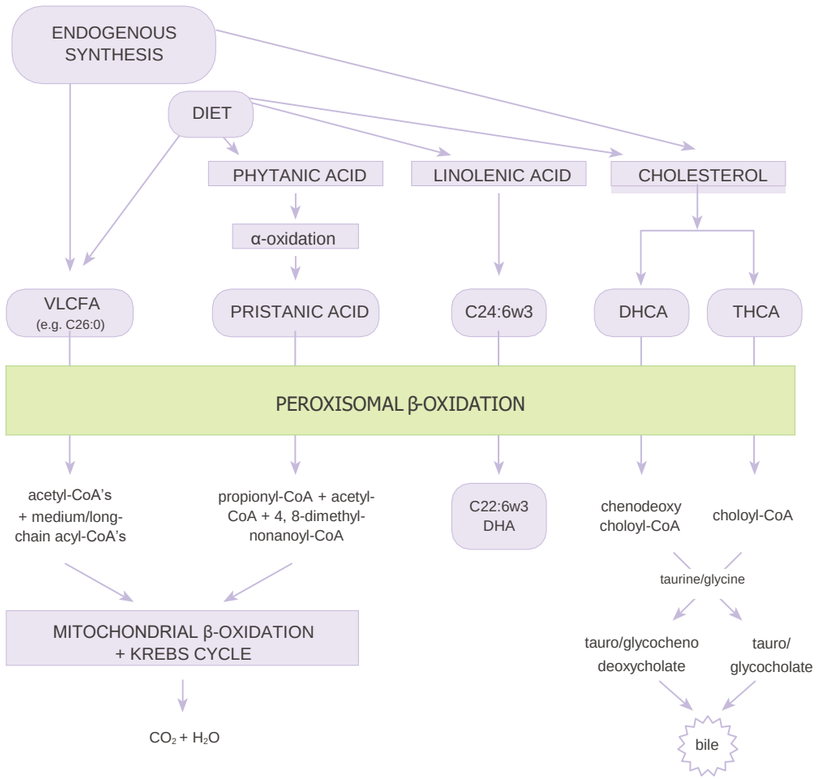
X-linked adrenoleukodystrophy (X-ALD) is one of the most common peroxisomal disorder, with a frequency rate between 1/20,000 and 1/50,000. Zellweger syndrome is one of the most common peroxisomal disorder found in early infancy. The disease is estimated to be found in one in every 50,000 to 100,000 newborns. Primary hyperoxaluria occurs at a frequency rate of 58,000 to one. Multiple cases of peroxisomal disorders have been reported in Korea as well. In January 2020, GC Labs has added metabolomes associated with peroxisomal disorders to the neonatal screening test (NST) items, including: C20:0, C22:0, C24:0, C26:0, C20:0-LPC, C22:0-LPC, C24:0-LPC, and C26:0-LPC. The addition is expected to raise the number of infants found or diagnosed with peroxisomal disorders in Korea.

The metabolism of phytanic acid and pristanic acid, and peroxisomal disorders

Mechanism of phytanic acid and pristanic acid accumulation in peroxisomal disorders

Phytanic acid is a 3,7,11,15-tetramethylhexadecanoic acid. It is a branched chain fatty acid acquired from dairy products, fat of ruminants, and specific fish. Unlike most fatty acids, phytanic acid is not metabolized by beta-oxidation. It is alpha-oxidated in peroxisome, and converted to pristanic acid by removing a single carbon. Pristanic acid is a 2,6,10,14-tetramethylpentadecanoic acid. Like phytanic acid, it is found in butter fat and fat stored in cows. For humans there are two sources of pristanic acid: meals, and the byproducts of phytanic acid alpha-oxidation. Pristanic acid forms medium chain fatty acid through multiple beta-oxidations. Medium chain fatty acid is converted to carbon dioxide and water in the mitochondrion.

If alpha-oxidation of phytanic acid is hindered by phytanoyl-CoA hydroxylase or peroxin-7 activity deficiency caused by *PHYH* mutation, phytanic acid is accumulated in plasma and tissues, which is called the Refsum disease. Likewise, in PBDs and other diseases, if beta-oxidation in peroxisome is hindered by genetic defects related to *PEX*, pristanic acid is accumulated in plasma and tissues.



Ref) Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases. Springer,2014:375-397

Fig. 1. Diagram Expression of the Role of Peroxisomal Beta-Oxidation System

Clinical usefulness of pristanic acid and phytanic acid

Need to understand various test methods for peroxisomal disorders

Individual peroxisomal disorders are highly rare, and the onset age widely ranges from the neonatal period to the adult period. Their symptoms are similar to those of more common disorders, which make them more difficult to diagnose. In addition, the various tests used to diagnose peroxisomal disorders require an understanding of complex and unfamiliar biochemical pathways, and numerous other diseases are involved in differentially diagnosing each peroxisomal disorder.

However, peroxisomal disorders have a number of common clinical manifestations, and are generally classified into four groups of clinical scenarios (Table 2).

Table 2. Classification of Peroxisomal Disorders Based on Clinical Scenarios

Group	Disease	Group	Disease
Group 1	PBDs(ZSD), PODs(Acyl CoA oxidase deficiency, D-bifunctional protein deficiency, etc.)	Group 3	X-ALD/AMN and phenotypic variants
Group 2	RCDP (RCDP1, RCDP2, RCDP3)	Group 4	Rest group (Refsum disease, Acatalasemia, Hyperoxaluria type 1, etc.)

Ref) Neurochem Res. 1999 Apr;24(4):565-580.

Table 3. Biochemical Characteristics of Peroxisomal Disorders

	Diagnostic group								
	1			2			3	4	
	ZSDs (ZS, NALD, IRD)	ACOX1D	DBPD	RCDP Type 1	RCDP Type 2	RCDP Type 3	X-ALD	RD	AMACRD
Plasma									
Very-long chain fatty acids	↑	↑	↑	N	N	N	↑	N	N
Di- and trihydroxy-cholestanoic acid	↑	N	↑[a]	N	N	N	N	N	↑
Phytanic acid	N-↑[b]	N	N-↑[d]	N-↑[b]	N	N	N	↑	N-↑
Pristanic acid	N-↑	N	N-↑[c]	N	N	N	N	N	↑
Erythrocyte membranes									
Plasmalogen level	↓	N	N	↓	↓	↓	N	N	N
Fibroblasts									
Plasmalogen synthesis	↓	N	N	↓	↓	↓	N	N	N
DHAPAT	↓	N	N	↓	↓	↓[d]	N	N	N
Alkyl DHAP synthase	↓	N	N	↓	N	↓	N	N	N
C26:0 ß-oxidation	↓	↓	↓	N	N	N	↓	N	N
Pristanic acid ß-oxidation	↓	N	↓	N	N	N	N	N	↓
Acyl-CoA oxidase 1	↓	↓	N	N	N	N	N	N	N
D-bifunctinoal protein	↓	N	↓	N	N	N	N	N	N
Phytanic acid α-oxidation	↓	N	N	↓	N	N	N	↓	N
Phytanoyl CoA hydroxylase	↓	N	N	↓	N	N	N	↓	N
Peroxisomes	Absent	Present but abnormal	Present but abnormal	Present	Present	Present	Present	Present	Present

ZSDs, Zellweger spectrum disorders; ZS, Zellweger syndrome; NALD, neonatal adrenoleukodystrophy; IRD, infantile Refsum disease; ACOX1D. acyl-CoA oxidase 1 deficiency; DBPD, D-bifunctional protein deficiency; RCDP, rhizomelic chondrodysplasia punctata; X-ALD, X-linked adrenoleukodystrophy; RD, Refsum disease; AMACRD, 2-methylacyl-CoA racemase deficiency; N, normal.

[a] Di- and trihydroxycholestanoic acid are not elevated in all DBPD-patients.

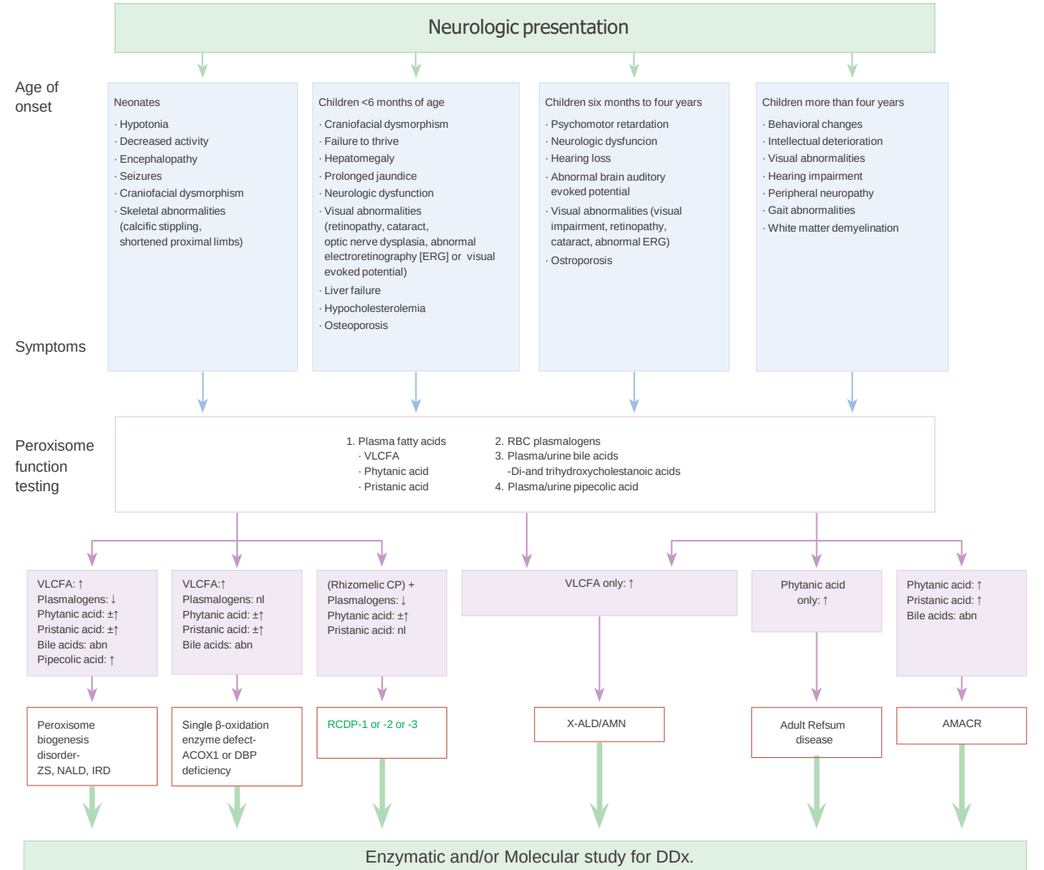
[b] Phytanic acid is derived from dietary sources only and may therefore vary from normal to elevated in patients in whom phytanic acid α-oxidation is deficient.

[c] Pristanic acid is derived from dietary sources only either directly or indirectly from phytanic acid via α-oxidation and may therefore vary from normal to elevated if pristanic acid β-oxidation is deficient.

[d] Phytanic acid is often elevated if pristanic acid β-oxidation is impaired even if phytanic acid α-oxidation per se is normal.

Ref) Biochim Biophys Acta. 2012 Sep;1822(9):1421-1429.

Clinical approach to peroxisomal disorder requires consideration of patients' onset ages. Fig. 2 lists the clinical manifestations that require suspicion and testing of peroxisomal disorders. Typical clinical manifestations include: hypotonia, lactation issues, loss of hearing/sight, psychomotor retardation, low and wide nasal bridge, hepatomegaly, seizure, and loss of white matter (leukodystrophy) caused by demyelination. Findings of biochemical peroxisome function tests include: increase in VLCFA concentration in plasma; increase in phytanic acid, pristanic acid, and pipecolic acid in plasma and fibroblast; decrease in plasmalogen in red blood cells; increase in DHCA/THCA concentration in plasma/urine; and bile acids production abnormalities. It is crucial for accurate diagnosis to comprehensively consider clinical symptoms, radiological tests, and biochemical peroxisomal function test results, narrow the scope of suspected peroxisomal disorders, and performing enzyme activity tests and molecular genetic tests for the most suspected disorders. Pathological biopsy can be also included if clinically required. However, as with all genetic disorders, the following diagnostic approach may have limitations for new diseases to be discovered in the future and patients with rare and atypical clinical manifestations.



Ref) Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed.: McGraw-Hill Education, 2017

Fig. 2. Diagnostic Approach to Peroxisomal Disorders with Neurological Clinical Symptoms

Interpretation and cautions for Phytanic Acid and Pristanic Acid Test Results

In general, phytanic acid concentration in plasma is known to increase in many PBDs (RCDP1, etc.) and Refsum disease. The plasma concentration of pristanic acid is known to increase in PBDs and DBP, AMACR, and SCPx deficiencies. As shown in Table 4, peroxisomal disorders can be differentially diagnosed based on phytanic/pristanic acid test results and pristanic/phytanic acid ratios. The diagnosis of peroxisomal disorders also require an interdisciplinary approach across multiple departments including detailed patient and family history, examination, clinical and biochemical findings, genetic tests, various radiologic tests, and expert opinions. As such, it would be more appropriate to use phytanic/pristanic acid test results as an aid to diagnose peroxisomal disorders using the aforementioned interdisciplinary approach rather than to independently use them to diagnose peroxisomal disorders.

Table 4. Differential Diagnosis for Phytanic and Pristanic Acid Increase in Plasma

Phytanic acid accumulation, pristanic acid normal		
No other disturbances	→	Classical Refsum disease
Plasmalogens deficient, unprocessed thiolase	→	Classical RCDP
Phytanic acid accumulation, pristanic acid accumulation		
Normal pristanic/phytanic acid ratio	→	Generalized peroxisomal disorder
Elevated pristanic/phytanic acid ratio	→	Bifunctional protein or thiolase deficiency

Ref) J Inherit Metab Dis. 1998 Oct;21(7):697-728.

In addition, in newborns, the plasma concentration of phytanic/pristanic acid may be normal even with partial defect in the alpha-oxidation of phytanic acid, because phytanic/pristanic acid is not produced by a human body *de novo* and exists only in small amounts in formulas and breast milk, and their plasma concentration is increased by food intake. Therefore, these factors need to be considered when interpreting test results.

Test Items Guide

Test Items	Specimen (mL)	Test date / time requirement	Test method	Insurance information
Phytanic acid (GC Labs code: S004)	EDTA P 2.0	Thu / 7 days	GC / MS	Nu 518 / D518002C
Pristanic acid (GC Labs code: D724)	EDTA P 2.0			-

Neonatal Screening Test Request Form

* The above information is as of October 1, 2021, and may change later. Please visit our website for the latest updates (http://www.gclabs.co.kr).

Testing Information

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References

1. Han-wook Yoo, Chapter 15. Peroxisome Metabolic Disorders, *Genetic Metabolic Disease Cases,* Korea Medical Book Publishing Company, 2016:655-685.
2. Bwee Tien Poll-The and Ronald J. A. Wanders. Peroxisomal Disorders.In: Nenad Blau, et al., editors. Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases. Springer,2014:375-397.
3. Ronald J.A. Wanders and William B. Rizzo. Inborn Errors of Peroxisome Biogenesis and Function. In: Kyriakie Sarafoglou, et al., editors. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed.: McGraw-Hill Education, 2017.
4. N. M. Verhoeven, R. J. A. Wanders, B. T. Poll-The, J.-M. Saudubray and C. Jakobs. The metabolism of phytanic acid and pristanic acid in man: A review. J Inherit Metab Dis. 1998 Oct;21(7):697-728.
5. Ronald J.A. Wanders. Peroxisomal Disorders: Clinical, Biochemical, and Molecular Aspects. Neurochem Res. 1999 Apr;24(4):565-80.
6. Bwee Tien Poll-The, Jutta Gärtner. Clinical diagnosis, biochemical findings and MRI spectrum of peroxisomal disorders. Biochim Biophys Acta. 2012 Sep;1822(9):1421-9.
7. P. Vreken, A.E.M. van Lint, A.H. Bootsma, H. Overmars, R.J.A. Wanders, A.H. van Gennip. Rapid stable isotope dilution analysis of very-long-chain fatty acids, pristanic acid and phytanic acid using gas chromatography–electron impact mass spectrometry.
8. J Chromatogr B Biomed Sci Appl. 1998 Aug 25;713(2):281-7.
9. http://www.uptodate.com
10. https://www.ncbi.nlm.nih.gov/books/NBK1448/

Clinical Microbiology Total Laboratory Automation and Automated Blood Culture Systems

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Automation is a key trend in modern society, and is also useful in clinical laboratories. Lab automation increases the efficiency of large-scale testing, drastically reduces the testing turnaround time (TAT), increases test precision and accuracy by reducing errors caused repetitive manual tasks, and minimizes the loss or swapping of specimens.

However, automation requires high initial installation costs, large spaces, and the development of relevant infrastructure. Previously, clinical lab automation only targeted clinical chemistry and diagnostic immunology tests using serum samples. In recent years, however, automation has spread to include other areas of laboratory medicine.

Clinical microbiology laboratories were traditionally notorious for their highly intensive manual workload. However, advancements in technology have allowed these labs to adopt total laboratory automation (TLA) and automated blood culture systems. For the first time in Korea, GCLabs adopted a microbiology TLA system: WASPLab® (bioMérieux, France) in order to provide rapid, accurate and high-quality test results.

Testing Process at Microbiology Laboratories (TLA System)

The traditional process for a clinical microbiology laboratory is as follows: specimen arrival, registration, inoculation, overnight incubation, and interpretation. The media and incubation times vary depending on the specimen type. After the incubation stage, if the culture comes out positive, the process continues to include identification and antimicrobial susceptibility testing before reporting the results.

The WASPLab® system is capable of handling the entire work-up range from specimen registration, inoculation, incubation, to interpretation (Fig. 1).

Fig. 1. Microbiology Laboratory TLA System (WASPLab®)

In particular, the system automatically obtains positive or negative results from the plates by using images, and allows the technician to conveniently check the results on the monitor. The system greatly improves the laboratory efficiency and allows for rapid results.

For the efficient use of WASPLab®, specimens must be in liquid form in a designated specimen container. Once the system is installed, GCLabs plans to apply a system for analyzing urine specimens.

Previously, the test took four days to get results. After applying this new system, the results will be reported within two days for negative results, or within three days for positive results, and includes bacterial identification and antimicrobial susceptibility tests. However, the specimen must be transported in a designated urine container (BD Vacutainer, etc.) for these rapid results.

Automated Blood Culture System

Bloodstream infections are one of the most serious infectious diseases. Bacteremia refers to the existence of bacteria in blood, which is diagnosed through blood culture. Blood cultures were manually performed in the past; today, automated blood culture systems are widely used. Manual blood cultures include processes such as observing samples for turbidity, hemolysis, gas generation, colonization, and other aspects of bacterial growth after seven days of incubation, which is followed by a blind subculture. In contrast, automated blood culture systems use commercial blood culture media to measure the CO2 concentrations, pH levels, and gas pressure on a regular basis as automatic confirmation of microbial growth.

Automated blood cultures are much more convenient than manual blood cultures, and especially as there is no need for a blind subculture. In addition, automated blood cultures reduce instances of false positives and pseudobacteremia, and increases the detection rates, thereby reducing the incubation time from seven days to five days. Automated blood culture systems widely used in Korea include the BACT/ALERT® VIRTUO® System (bioMérieux, France)

Fig. 2. Automated Blood Culture System (VIRTUO® System)

Using an automated blood culture system, the incubation time for blood cultures is five days. In typical cases, aerobic bacteria are detected within 12 h to 36 h, and anaerobic bacteria within 48 h to 72 h. An additional day or two may also be required for identification and susceptibility testing. Numerous factors affect the positive rate of blood culture. However, blood volume is the most important factor, and the BACT/ALERT® VIRTUO® System, which GCLabs have adopted, can measure the blood volume.

References

1. Korean Society of Diagnostic Immunology, *Diagnostic Immunology, 6th Edition,* Beommun Education. 2021
2. biomerieux, https://www.biomerieux-diagnostics.com/wasplab-microbiology-optimization

Positive Rate of Blood Culture and Hospital-acquired Infection in 2020

1. Positivity Rate of Blood Cultures

Sepsis is a serious infectious disease. The rapid detection of pathogens through a blood culture is highly crucial for the diagnosis, prognosis, and successful treatment of sepsis. GCLabs uses the latest model of automated blood culture systems, BACT/ALERT® VIRTUO®, for rapid bacteremia diagnoses. The system provides 24 h monitoring to enable real-time positivity detection and rapid results.

The recommended contamination rate of blood cultures is below 3%, and the recommended blood volume is 10.0 mL or more for adults. GCLabs monitors the monthly positive rates and contamination rates. We also monitor the blood volume and provide a comment if it drops below 5.0 mL. The following is a list of bacteria isolates and their positivity rates from blood cultures.

Table 1. List of bacteria isolates and its positive rate from blood culture

No.	*Organisms*	No. of isolates	%
1	*Escherichia coli*	2,976	24.6
2	*Staphylococcus epidermidis*	1,386	11.4
3	*Klebsiella pneumoniae*	828	6.8
4	*Staphylococcus hominis*	752	6.2
5	*Staphylococcus aureus*	731	6.0
6	*Staphylococcus capitis*	558	4.6
7	*Staphylococcus caprae*	351	2.9
8	*Enterococcus faecium*	318	2.6
9	*Bacillus species*	280	2.3
10	*Staphylococcus haemolyticus*	279	2.3
11	*Proteus mirabilis*	246	2.0
12	*Enterococcus faecalis*	239	2.0
13	*Pseudomonas aeruginosa*	176	1.5
14	*Corynebacterium species*	174	1.4
15	*Corynebacterium striatum*	153	1.3
16	*Acinetobacter baumannii complex*	137	1.1
17	*Streptococcus agalactiae*	113	0.9
18	*Staphylococcus pettenkoferi*	108	0.9
19	*Candida albicans*	104	0.9
20	*Candida parapsilosis*	98	0.8
21	*Enterobacter cloacae complex*	95	0.8
22	*Serratia marcescens*	80	0.7
23	*Candida glabrata*	76	0.6
24	*Clostridium perfringens*	74	0.6
25	*Bacillus cereus*	74	0.6
26	*Staphylococcus simulans*	60	0.5
27	*Candida tropicalis*	60	0.5
28	*Staphylococcus warneri*	57	0.5
29	*Stenotrophomonas maltophilia*	51	0.4
30	*Micrococcus luteus*	48	0.4
Total (Inclusive the other organisms)		12,108	100.0

Table 2. Monthly Positive Rate and Contamination Rate (%)

2020	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Average
positive rate (%)	10.8	11.9	13.5	14.1	14.2	16.5	15.8	19.4	18.1	17.2	16.8	14.0	15.1
Contamination rate (%)	4.4	4.0	4.4	4.8	5.8	7.3	4.9	7.5	6.0	5.8	5.6	5.0	5.5

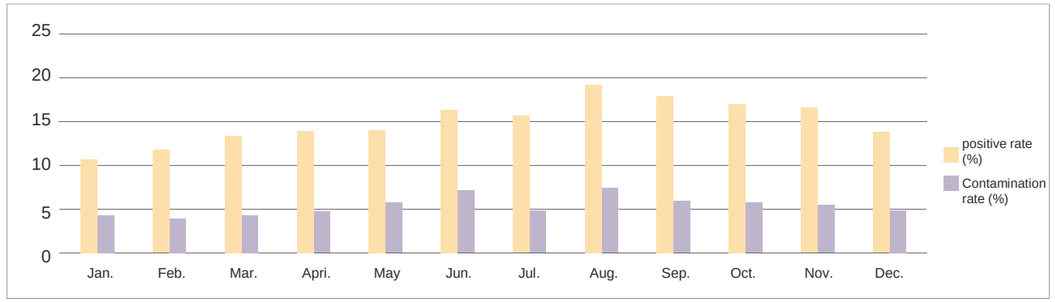
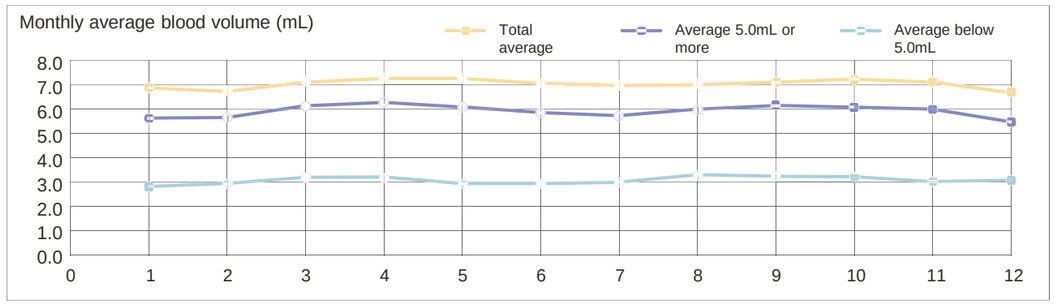
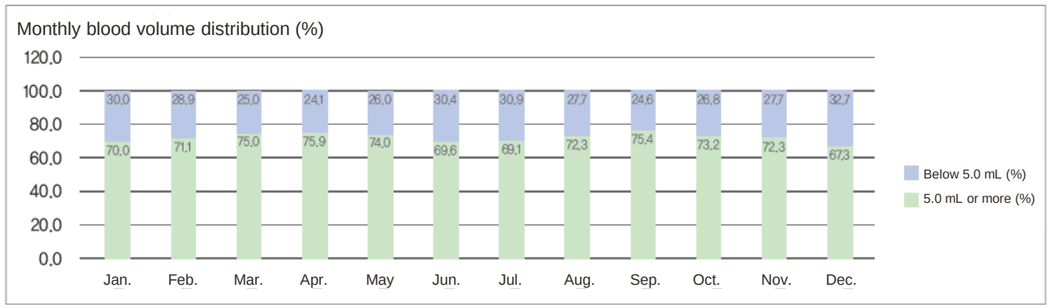


Table 3. Blood volume monitoring

Blood volume (mL)		Jan.	Feb.	Mar.	Apri.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Average
Overall average		5.7	5.7	6.2	6.3	6.2	5.8	5.8	6.0	6.2	6.1	6.0	5.5	5.9
5.0mL or more	Average	6.9	6.8	7.1	7.3	7.3	7.1	7.0	7.0	7.1	7.2	7.2	6.7	7.0
	%	70.0	71.1	75.0	75.9	74.0	69.6	69.1	72.3	75.4	73.2	72.3	67.3	71.8
5.Below 0mL	Average	2.8	2.9	3.2	3.2	3.0	3.0	3.0	3.3	3.3	3.3	3.1	3.1	3.1
	%	30.0	28.9	25.0	24.1	26.0	30.4	30.9	27.7	24.6	26.8	27.7	32.7	28.8





2. Positive rate of hospital-acquired infection

GCLabs monitors hospital-acquired infections (HAIs) according to the infectious disease guidelines of the Korea Disease Control and Prevention Agency (KCDC) in order to identify the number of patients, enabling them to implement effective preventive measures to take rapid action. Table 5 shows the diagnostic criteria for HAIs, and Table 6 shows the positivity rates of HAIs in 2020.

Table 4. Classification of legal communicable diseases

Classification	Class 1 Infectious Disease	Class 2 Infectious Disease	Class 3 Infectious Disease	Class 4 Infectious Disease
Characteristics	Infectious diseases with high risk of biological terrorism or fatality rates or risks of cluster infection, and requires reporting and high-level isolation including negative pressure isolation upon occurrence or spreading (17)	Infectious diseases requiring reporting and isolation within 24 hours upon occurrence or spreading, in consideration of possible communication (21)	Infectious diseases requiring reporting and isolation within 24 hours upon occurrence or spreading, due to the need for continuous monitoring (26)	Infectious diseases requiring sample monitoring for epidemic determination (23)
Type	A. Ebola virus disease B. Marburg fever C. Lassa fever D. Crimean congo hemorrhagic fever E. South America hemorrhagic fever F. Lift valley fever G. Smallpox H. Pest I. Anthrax J. Botulism K. Tularemia L. Emerging infectious disease syndrome M. SARS N. MERS O. Avian influenza infection human P. Novel influenza Q. Diphtheria	A. Tuberculosis B. Chickenpox C. Measles D. Cholera E. Typhoid F. Paratyphoid G. Bacillary dysentery H. Enterohemorrhagic escherichia coli infection I. Hepatitis A J. Pertussis K. Epidemic parotitis L. Rubella M. Polio N. Meningococcal infection O. Haemophilus influenzae B P. Pneumococcus infection Q. Hansen's disease R. scarlet fever S. Vancomycin resistant staphylococcus aureus (VRSA) infection T. Carbapenem resistant enterobacteriaceae (CRE) infection U. Hepatitis E	A. Tetanus B. Hepatitis B C. Japanese encephalitis D. Hepatitis C E. Malaria F. Legionella disease G. Vibrio vulnificus septicemia H. Camp fever I. Endemic typhus J. Tsutsugamushi K. Leptospirosis L. Brucellosis M. Rabies N. Hemorragic fever related renal syndrome O. AIDS P. Creutzfeldt-Jakob disease (CJD) and Variant CJD (vCJD) Q. Yellow fever R. Dengi fever S. Q fever T. West Nile fever U. Lime disease V. Tick-borne encephalitis W. Melioidosis X. Chikungunya fever Y. Severe fever with thrombocytopenia syndrome virus (SFTS) Z. Zika virus infection	A. Influenza B. Syphilis C. Ascariasis D. Trichuriasis E. Enterobiasis F. Clonorchis sinensis G. Paragonimiasis H. Fasciolopsis buskii I. Hand-foot-and-mouth disease J. Gonorrhea K. Chlamydia infection L. Chancroid M. Herpes simplex genitalis N. Condyloma acuminata O. Vancomycin-resistant enterococc (VRE) infection P. Methicillin-resistant Staphylococcus aureus (MRSA) infection Q. Multidrug-resistant Pseudomonas aeruginosa (MRPA) infection R. Multidrug-resistant Acinetobacter baumannii (MRAB) infection S. Intestinal infectious disease T. Acute respiratory infection U. Imported parasite disease V. Enterovirus Infection W. Human papilloma virus infection

Ref) Korea Disease Control and Prevention Agency, *Classification and Types of Statutory Infectious Diseases (Jul, 2020)*

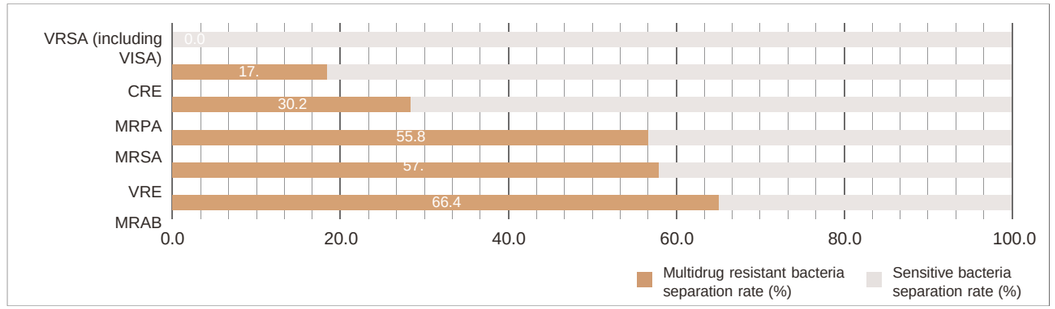
Table 5. Diagnostic criteria for hospital-acquired infections

Class	Infectious disease	Diagnostic criteria
Class 2	Vancomycin-resistant staphylococcus aureus (VRSA) infection	Isolation and identification of vancomycin-resistant (I or R) staphylococcus aureus in clinical specimen
	Carbapenem resistant enterobacteriaceae (CRE) infection	Isolation and identification of carbapenam resistant enterobacteriaceae in clinical specimen
Class 4	Multidrug-resistant Pseudomonas aeruginosa (MRPA) infection	Isolation and identification of multidrug Resistant Acinetobacter baumannii in clinical specimen (confirm resistance to carbapenem, aminoglycoside, and fluoroquinolone)
	Multidrug-resistant Pseudomonas aeruginosa (MRPA) infection	Isolation and identification of multidrug Resistant Pseudomonas aeruginosa in clinical specimen (confirm resistance to carbapenem, aminoglycoside, and fluoroquinolone)
	Methicillin-resistant Staphylococcus aureus (MRSA) infection	Isolation and identification of oxacillin or cefoxitin-resistant (R) staphylococcus aureus in clinical specimen
	Vancomycin-resistant enterococc (VRE) infection	Isolation and identification of vancomycin-resistant (R) enterococcus in clinical specimen

Ref) Korea Disease Control and Prevention Agency, *2020 Medical Infectious Disease Control Guidelines*

Table 6. List of hospital-acquired infection isolates and their positivity rates

Multidrug resistant bacteria	No. of separated mycetoma	No. of multidrug resistant mycetoma	Multidrug resistant bacteria separation rate (%)
MRAB	5,443	3,612	**66.4**
VRE	20,268	11,733	**57.9**
MRSA	7,603	4,245	**55.8**
MRPA	13,195	3,990	**30.2**
CRE	84,157	15,083	**17.9**
VRSA / VISA	7,603	0	**0.0**



Q&A

Testosterone

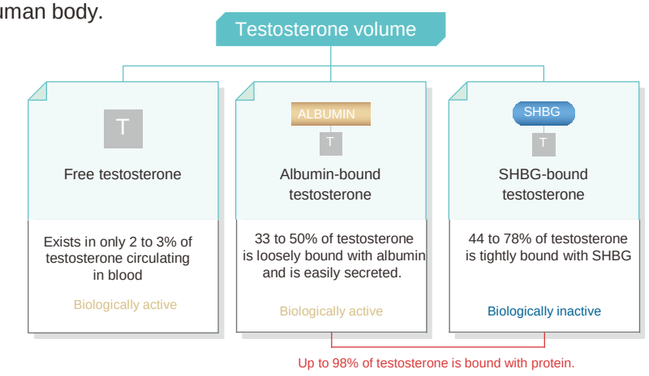
1 What is testosterone?

As the most widely known male hormone, testosterone affects the external genitalia development and the secondary sexual character of men. In women, it serves as a precursor for estrogen. Testosterone also causes anabolic effects that affect the cell growth and division of various organs and tissues and the synthesis of various substances in both men and women.

Men's blood testosterone begins to increase at the age of 10, and plateaus between 20 and 40 before decreasing. Women have 5 to 10% of testosterone in men. However, it plays a crucial role in maintaining muscle and bone tissues, and also affects the distribution of body fat, energy level maintenance, sexual desire, and virilism.

2 How is total testosterone different from free testosterone?

98% of testosterone is bound with specific protein. Its activity differs depending on which protein it is bound with. 60% of testosterone circulating in blood is bound with sex hormone binding globulin (SHBG), and only 40% is bound with albumin. 2 to 3% of testosterone is not bound with any protein (free testosterone). Only free testosterone and testosterone loosely bound with albumin are biologically active within a human body.



Ref) Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 6th ed. Pp. 1617~1654

Fig.1. Different testosterone by the type of bound protein

Total testosterone is typically used to assess male hormones. However in cases where total testosterone is close to the bottom of the normal range or changes in SHBG are suspected, free testosterone may be helpful in assessing the biological activity of testosterone.

3 What are the diseases identifiable using testosterone test results, and how do I interpret the results?

In men, low testosterone is typically found along with hypogonadism, and may be associated with fatigue, energy decline, and loss of sexual desire. High testosterone may be found in patients with testicle cancer or resistance to androgen, or patients using steroid drugs.

In women, excessive testosterone is associated with various types of virilism including hirsutism, pimples, amenorrhea, and infertility. Increase in testosterone may be identified in patients with polycystic ovarian syndrome or tumor in the ovary or adrenal.

Testosterone level changes in the course of a day. In case of a young adult, the level peaks at 08:00 a.m. and hits the bottom at 08:00 p.m. The scope of change decreases as one grows older. It is easier to determine whether testosterone level is normal or decreased when the level is higher. For this reason, testosterone levels are typically measured between 07:00 and 10:00 a.m. Interpretation of the test results needs to comprehensively consider various factors including measurements taken twice or more on different days after fasting in the morning, related symptoms, and the results of various related tests.

Test Items Guide

Test Items	Specimen (mL)	Test date / time requirement	Test method	Insurance information	Note
Testosterone (GC Labs code: L959)	Serum 0.5	Mon-Tue / 1 day (night test)	CMIA	Nu 371 / D3710063	-
Free testosterone (GC Labs code: P767)	Serum 1.0	Mon-Fri / 7 days	CIA	Nu 371 / D3710053	-
Total & Free testosterone (men) (GC Labs code: P776)	Serum 1.0		-	-	set test (P776, L959, P767)

* The above information is as of October 1, 2021, and may change later. Please visit our website for the latest updates (http://www.gclabs.co.kr).

GC Labs 39th Anniversary

“To Widen the Horizon of the Diagnostic Test Market”

On July 1, GC Labs celebrated its 39th anniversary. The ceremony was held in compliance with the government’s COVID-19 guidelines, by minimizing attendees and organizing online lives streaming. At the ceremony, achievement awards, long-term service awards, and exemplary awards were given to 51 outstanding employees.

GC Labs was founded in 1982 as Korea’s first medical institution specializing in diagnostic testing. Now, the 39-year-old institution is one of the best clinical test providers in Korea. All of us at GC Labs will give our all to join our wisdom to build strategies, and stay true to GC Labs history of challenging the status quo.

Partnership agreement signed with KNCV Tuberculosis Foundation for enhanced TB treatment safety monitoring

On August 18, GC Labs signed a partnership agreement with the KNCV Tuberculosis Foundation for a joint project on “enhanced TB treatment safety monitoring” in Kyrgyzstan and Vietnam.

The project is aimed at quality management of non-bacterial tests including blood tests that play important roles in monitoring the status of patients starting TB treatment. The signing of the agreement will contribute to the KNCV’s efforts to achieve its goal of “TB eradication and safer TB treatment.”

GC Labs holds outstanding research experience in clinical diagnosis across Asia, and will leverage the strength to help the world eradicate TB, and continue its efforts to fulfill its social responsibility as Korea’s first medical institution specializing in diagnostic testing.

Academic Activities

Paper

Eun-hee Lee, CEO

Molecular psychiatry 2021 doi: 10.1038/s41380-021-01185-z.

Correction: Astrocytic water channel aquaporin-4 modulates brain plasticity in both mice and humans: a potential gliogenetic mechanism underlying language-associated learning

J Woo, J E Kim, J J Im, J Lee, H S Jeong, S Park, S- Y Jung, H An, S Yoon, S M Lim, S Lee, J Ma, E Y Shin, Y- E Han, B Kim, E H Lee, L Feng, H Chun, B- E Yoon, I Kang, S R Dager, I K Lyoo, C J Lee

Kyutaeg Lee, Specialist, Laboratory Medicine

1.Laboratory Medicine and Quality Assurance 2021;43(2):94-106

Survey of the Referral Laboratory Sample Managements of Medical Clinics in Jeju Island

Moo-Sang Chong, Kyutaeg Lee

2.Korean Journal of Clinical Laboratory Science 2021;53:137-142

The Patterns of Acquiring Anti-Mycobacterial Drug Resistance by Susceptible Strains of Mycobacterium tuberculosis

Kyutaeg Lee, Moo-Sang Chong

Jiwon Lee, Laboratory Medicine

PLOS ONE 2021;16(6):e0253541. DOI: 10.1371/journal.pone.0253541

Immunoglobulin gene rearrangement in Koreans with multiple myeloma: Clonality assessment and repertoire analysis using next-generation sequencing

Miyoung Kim, Kibum Jeon, Kasey Hutt, Alyssa M Zlotnicki, Hyo Jung Kim, Jiwon Lee, Han-Sung Kim, Hee Jung Kang, Young Kyung Lee

Yura Jun, Laboratory Medicine

Laboratory Medicine Online 2021; 11(3): 155-161

A Study for Accurate Reporting of Bacteria in Urine by Manual Microscopic Examination

You La Jeon, Woo-In Lee, So Young Kang, Myeong Hee Kim

Rihwa Choi, Laboratory Medicine

Clinical Laboratory 2021;67:1741-1745

Association Among Glycemic Biomarkers in Korean Adults: Hemoglobin A1c, Fructosamine, and Glycated Albumin

Rihwa Choi, Mi-Jung Park, Sukjung Lee, Sang Gon Lee, Eun Hee Lee

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