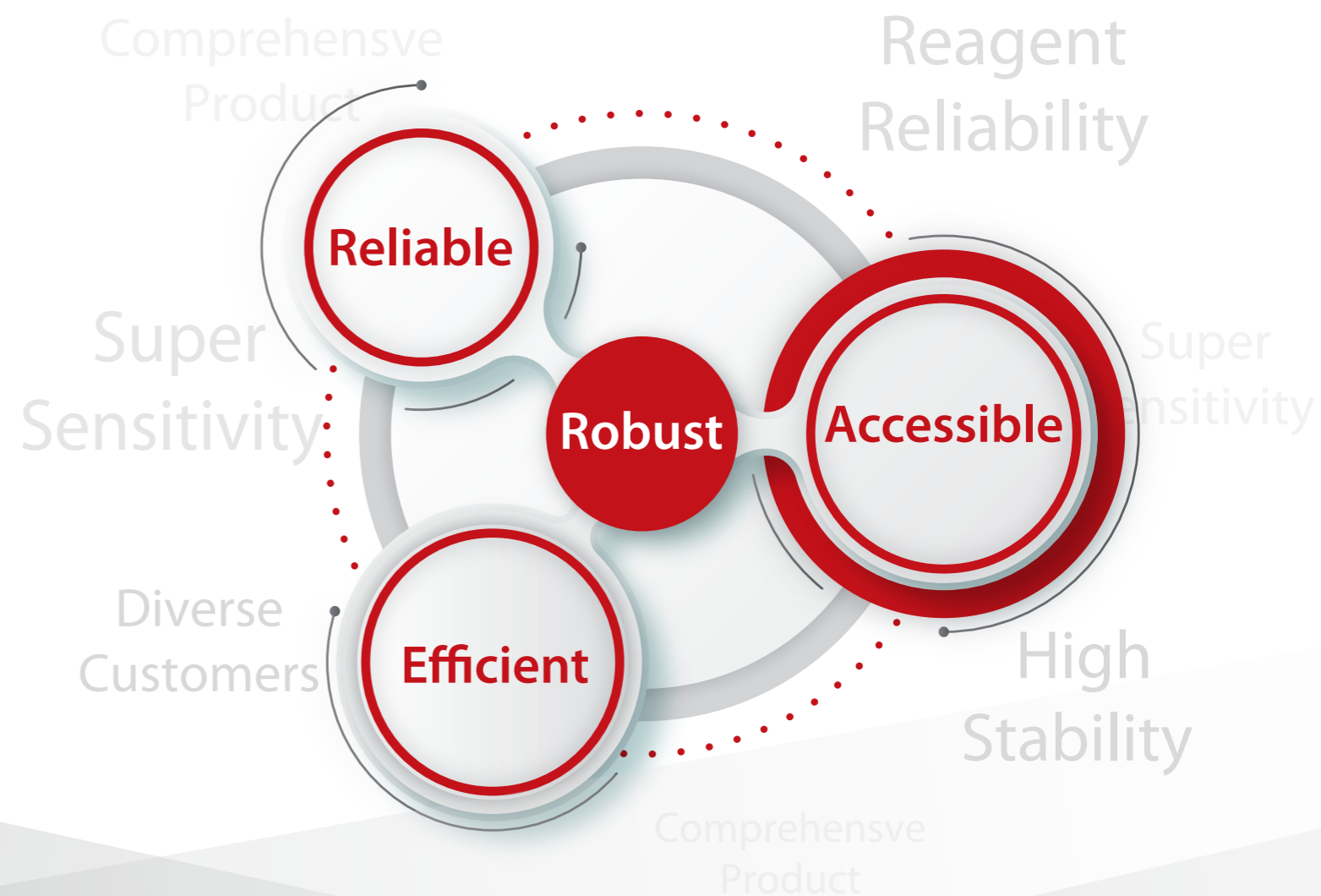


CLIABook

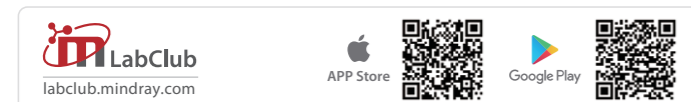
Discover the clinical applications of high medical value biomarkers



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www.mindray.com

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Preface – High Medical Value Biomarkers



Tina Liu, Ph.D, Mindray Clinical Academic Manager

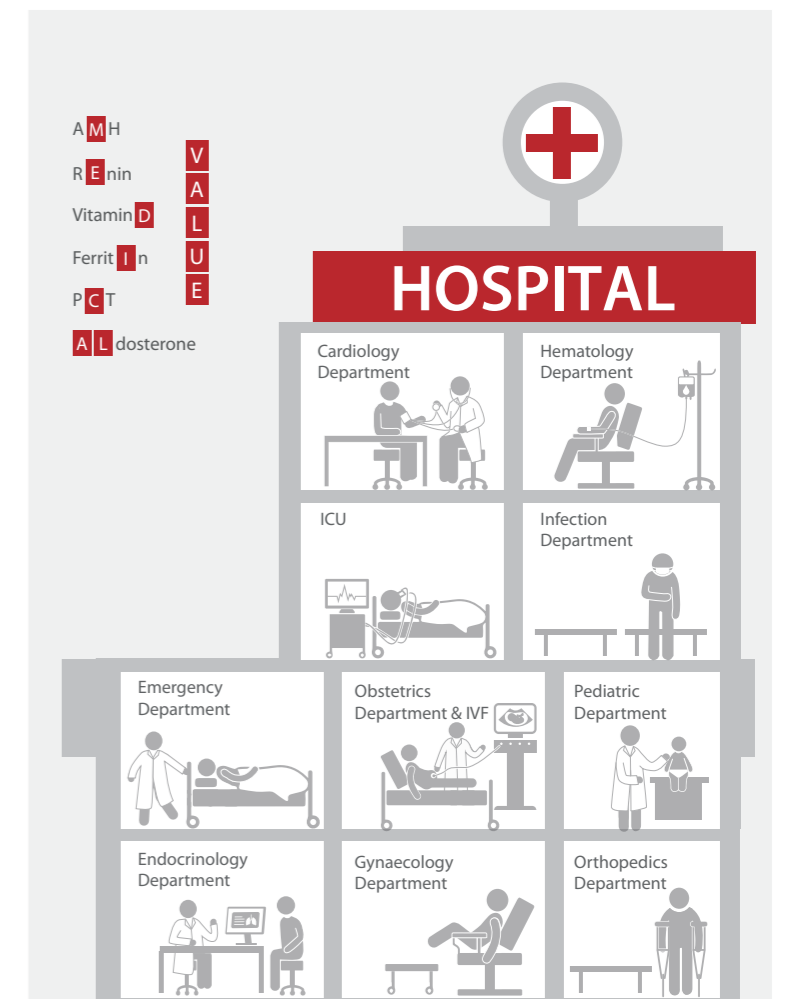
There are several definitions of biomarkers. A biomarker is a characteristic that can be objectively measured and evaluated as a physiological indicator as well as a pathological response to a therapeutic intervention. A biomarker test can be as simple as a laboratory test and a biomarker can be as complex as a pattern of genes or proteins. In practical terms, biomarkers, especially what we call high medical value biomarkers, can specifically and sensitively reflect the disease state. In this way, it can on the one hand guide disease diagnosis, and on the other help with disease monitoring during and following treatment.

Biomarkers can be divided into four broad categories:

- 1) Diagnostic biomarkers: categorize patients by presence or absence of disease/disease subtype
- 2) Prognostic biomarkers: provide information on the likely course of disease in an untreated diagnosed individual (future outcome of a disease)
- 3) Predictive biomarkers: categorize patients by their likelihood of response to a particular treatment
- 4) Response/pharmacodynamic biomarkers: indicate a biological response in patients after patients receiving treatment interventions

Mindray has developed a group of high medical value biomarkers to provide high quality and high medical value CLIA solutions for supporting diagnosis-to-treatment management in different scenarios. This book is an introduction to the clinical values and clinical applications of these biomarkers which have almost all of the characteristics mentioned above. For instance, procalcitonin (PCT) is an important host response biomarker indicative of infection. For medical emergency, it can be used as an important biomarker for screening and early diagnosis of sepsis and indicating the severity of the infection. Meanwhile, in COVID-19 diagnosis, it can also be an essential biomarker to help clinicians exclude bacterial infection. Besides, monitoring PCT helps to avoid abuse of antibiotics and allows physicians to evaluate the treatment effectiveness more easily. Therefore, PCT is not only a diagnostic and prognostic biomarker, but also a predictive and pharmacodynamic biomarker.

This book describes the values and functions of some high medical value biomarkers for different diseases in different regions and clinical applications. It provides a full picture of how these biomarkers play significant roles in the occurrence, development, treatment and prognosis of diseases. Clinicians and lab professionals can turn to this book whenever they need to use any of these biomarkers to determine the patient's disease state and the therapeutic efficacy and thereby make the right medical decisions.



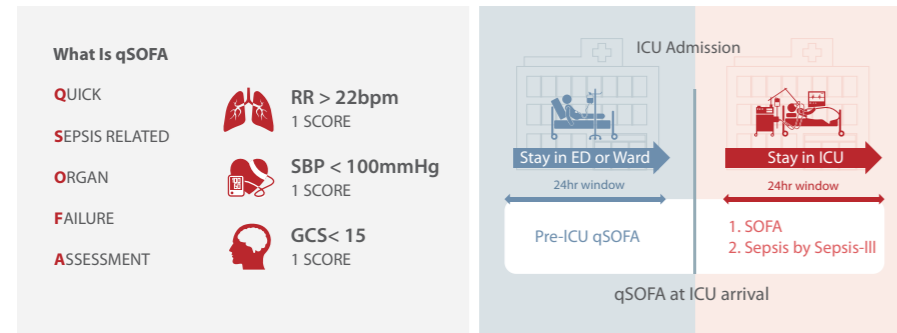
PCT – A Comprehensive Biomarker for Infection

Procalcitonin (PCT) is a precursor of calcitonin. PCT test is the only FDA-approved laboratory test specific to bacterial infection and sepsis diagnosis. PCT testing could provide information about the host response to bacterial infection.

PCT helps in the differentiation of viral and bacterial infections for early diagnosis and treatment.

One of the most promising functions of PCT test is the early detection of patients at risk for sepsis and bacteremia.

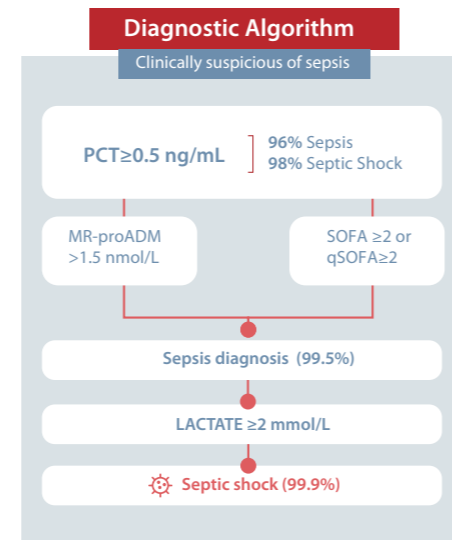
For medical emergency, screening and early diagnosis of sepsis are significantly helpful for the patient management. The diagnosis of sepsis should be based on evidence from the patient's symptoms and signs, as well as sepsis specific laboratory tests, e.g., PCT and blood culture^[1]. Scores such as sequential organ failure assessment (SOFA) and quick SOFA (qSOFA) are also widely applied to support the diagnosis of sepsis^[2].



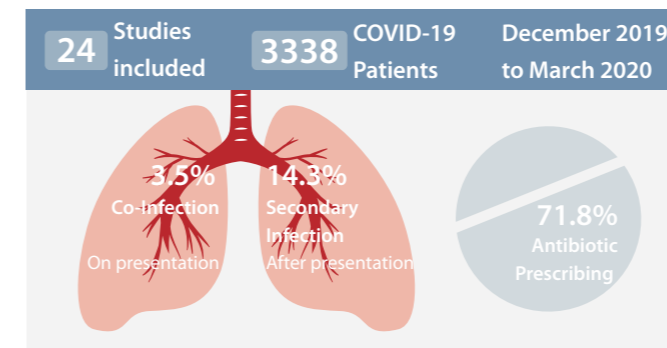
PCT can be combined with related clinical scores, including SOFA and qSOFA scores, for sepsis diagnosis and prognosis prediction. A simple modification of



qSOFA score by adding the ordinal scale of PCT value to qSOFA can greatly improve the suboptimal sensitivity problem of qSOFA and may serve as a quick screening tool for early identification of sepsis^[3].

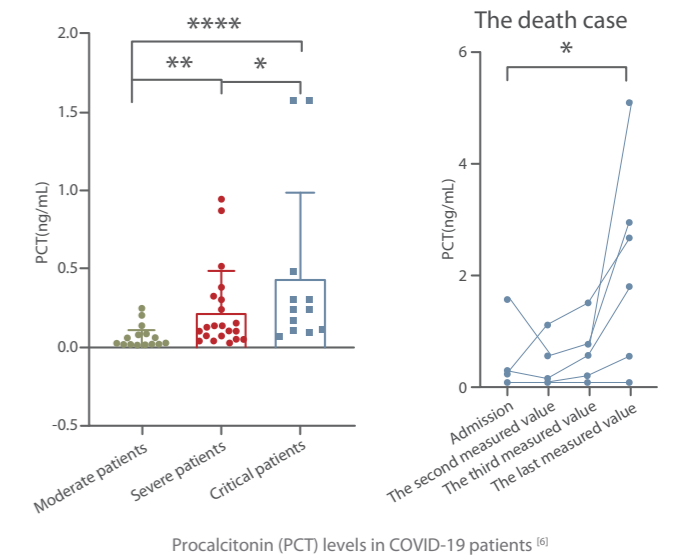


In addition, the clinical application of PCT in COVID-19 has become a hot topic among researchers. Some studies found bacterial coinfection and secondary infection happen in COVID-19 patients, and the frequency of bacterial infection is higher in critically ill patients than the mild/moderate ones^[4]. If a patient with COVID-19 also has bacterial co-infection or secondary infection not known to the clinician, the patient's life will be threatened by not only COVID-19 but also potential sepsis or septic shock. Hence, it is critical for clinicians to take into account comprehensive information when designing a treatment plan for a COVID-19 patient. Specifically, they should include PCT as a routine test before admitting the patient and use the test results as supplementary information to guide the treatment.



Acute bacterial co-infection in COVID-19 by a rapid living review and meta-analysis

With further research, clinicians found that PCT is a robust indicator for discriminating between critically ill and severe/moderate patients^[5]. PCT may be an indicator of disease severity in COVID-19. Moreover, serial PCT measurements may be useful in predicting the prognosis of COVID-19.



Procalcitonin (PCT) levels in COVID-19 patients^[6]



Blood culture
Gold standard for definitive diagnosis of bacterial and fungi infection



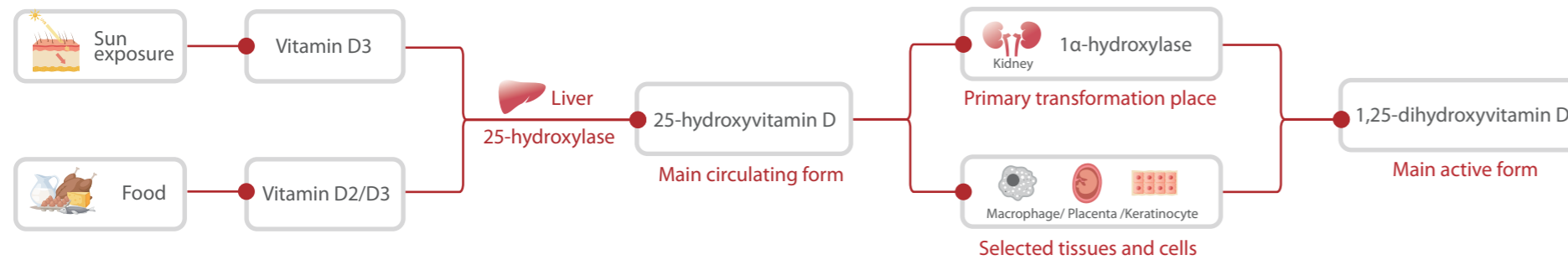
Clinical scores
A valuable tool to predict clinical response in sepsis



PCT
• Provide reliable pathogen -evidence
• Provide guidance for antibiotic therapy

Biomarker has characteristic that reflects the severity or presence of some disease state while the ideal biomarker of infection needs to be sensitive, specific, rapid and cheap. Early recognition, assessment of severity, and rapid detection of the causative microorganism are critical for early treatment and medication guidance. Mindray could provide comprehensive solutions including PCT assay, clinical scores and blood culture.

Multi-functional Steroid Hormone - Vitamin D



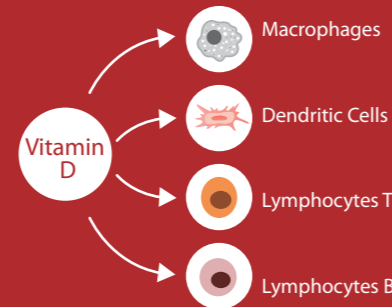
Vitamin D is a kind of fat-soluble vitamin. It is a steroid derivative and is an essential nutrient and indicator for human health.

The liver and other tissues metabolize vitamin D, whether from the skin or oral ingestion, to 25-hydroxyvitamin D, the principal circulating form of vitamin D. 25-hydroxyvitamin D is then further metabolized to 1,25-dihydroxyvitamin D principally in the kidney or in selected tissues and cells. 1,25-dihydroxyvitamin D is the main active form of vitamin D, responsible for most of its biologic actions.

Knowledge of the widespread effects of vitamin D on skeletal and non-skeletal functions, including immune functions, has developed considerably over the past decades.

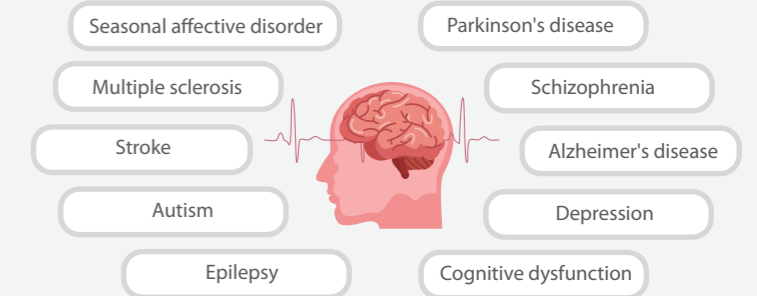
Vitamin D in Immune System

The role of vitamin D in innate and specific immune response has been proven in many studies. Vitamin D receptors (VDR) are present in many immunological cells, such as B cells, T cells and macrophages, mainly after immune response activation. Therefore, vitamin D deficiency is associated with increased susceptibility to infections like acute respiratory tract infections and severity of respiratory infections^[7]. Nowadays, more and more researches have further proven that vitamin D low levels are associated with adverse outcomes in COVID-19 patients because it plays an important role in immune system.



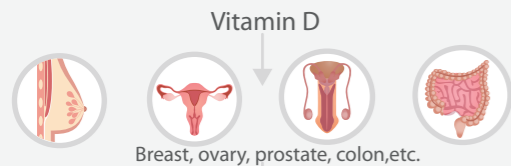
Vitamin D in Brain Health

Vitamin D interacts with the VDR in neuronal and glial cells resulting in the regulation of a variety of genes and metabolic processes that influences brain development, neurotransmission, neuroprotection amongst other functions^[10]. Vitamin D deficiency has serious long-lasting consequences for mental health and has been associated with a variety of neurological disorders.



Vitamin D in Cancer Progression

Accumulating data suggest that vitamin D can regulate the entire process of tumorigenesis, from initiation to metastasis and cell-microenvironment interactions. Vitamin D plays a key role in preventing the initiation stage by exerting anti-inflammatory and antioxidant defenses and DNA damage repair processes. Vitamin D deficiency increases the risk of developing cancer and vitamin D supplements might be an economical and safe way to reduce cancer incidence and improve cancer prognosis and outcome^[8].

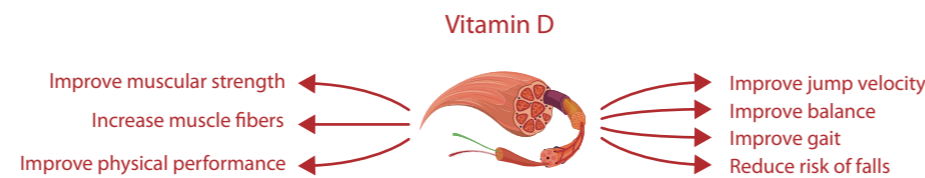


Cell Growth Regulation

- Apoptosis
- Anti-proliferation
- Pro-differentiation
- Autophagic cell death
- Antioxidant & DNA damage repair
- Antiangiogenic effect

Vitamin D in Neuromuscular Function

The general nature of vitamin D receptor (VDR) has led to new researches exploring the effects of vitamin D on a variety of tissues, especially skeletal muscles. The active form of vitamin D, calcitriol, acts in myocytes through genomic effects involving VDR activation in the cell nucleus to drive cellular differentiation and proliferation. Vitamin D deficiency is consistently associated with decrease in muscle function and increase in disability. Therefore, vitamin D supplementation can improve muscle strength and gait in different settings^[9].



Vitamin D in Cardiovascular Effects

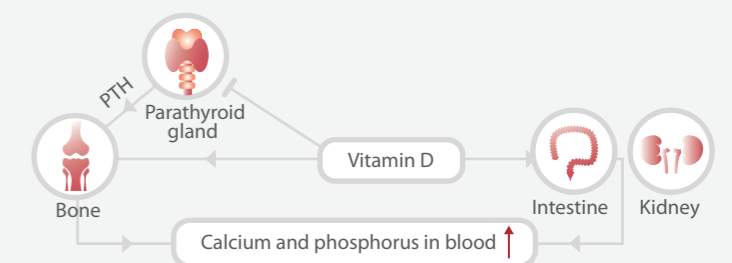
Vitamin D deficiency has emerged as an independent risk factor for cardiovascular mortality due to its association with structural and functional cardiovascular changes. Vitamin D deficiency could cause myocardial hypertrophy, inappropriate stimulation of the renin-angiotensin system and high blood pressure which seem to be linked to increased renin-angiotensin activity^[11]. Therefore, vitamin D supplements can potentially be beneficial to treat chronic kidney disease and to reduce the associated cardiovascular risk.



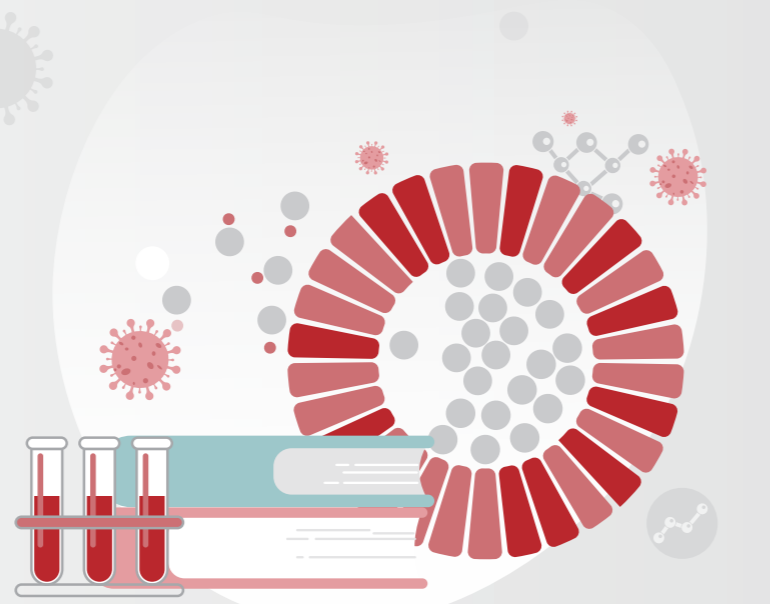
Vitamin D in Bone Health

Vitamin D is essential for strong bones, because it helps the body use calcium from the diet. Traditionally, vitamin D deficiency has been associated with rickets, a disease in which the bone tissue does not properly mineralize, leading to soft bones and skeletal deformities. Vitamin D deficiency can lead to osteomalacia and osteoporosis in adults^[13].

Role of vitamin D in the regulation of Ca and P

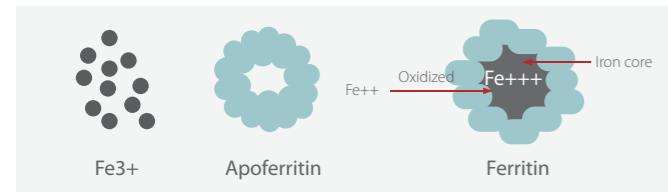


Wide Clinical Applications of Ferritin

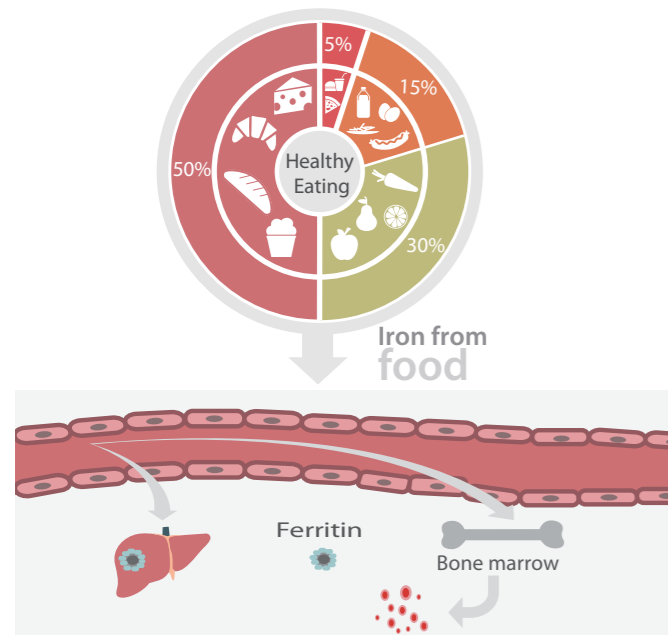


What is ferritin?

Ferritin is the protein which stores iron in human body.



The body absorbs iron from food. The absorbed iron is primarily used for red blood cell production, while the remaining iron is stored as ferritin in liver, spleen, and muscles etc.

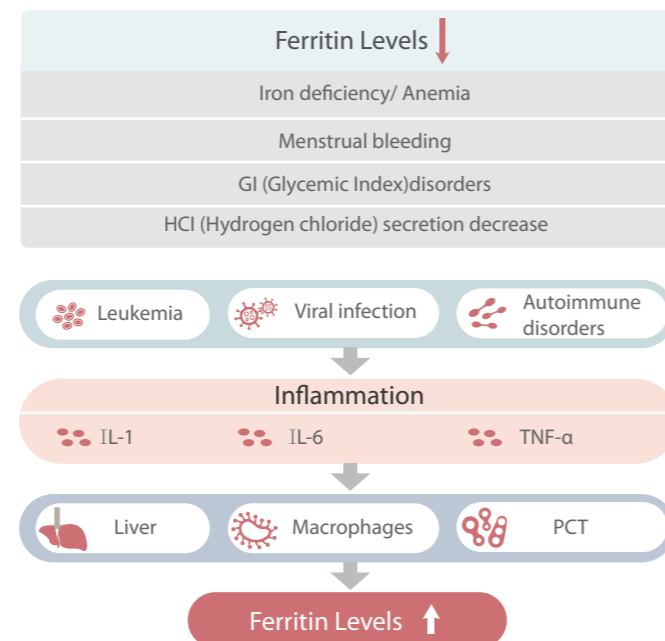


Iron is very important to the way the body works.



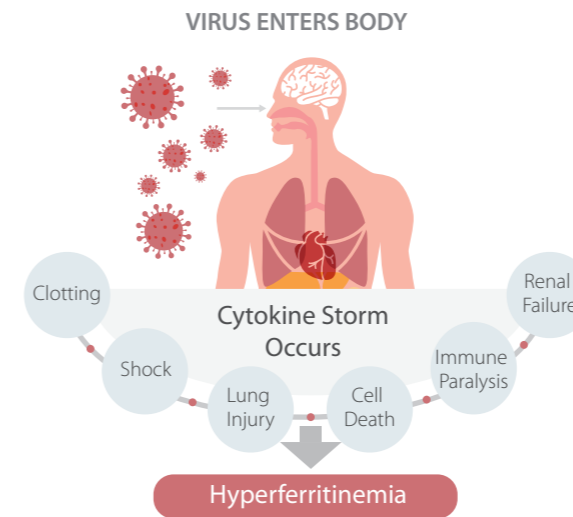
The change of ferritin levels

Different medical conditions could lead to different serum ferritin levels in human body.



The role of serum ferritin in COVID-19

Many studies on COVID-19 have revealed that elevated levels of ferritin are present in severe COVID-19 patients compared with non-severe ones. It has been concluded that serum ferritin levels are closely related to the severity of COVID-19^[14].



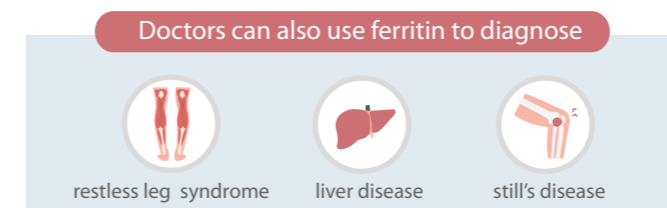
Thus, hyperferritinemia has been associated with increased illness severity and adverse outcomes in COVID-19^[15].

Ferritin blood test

To monitor a clinical condition, a ferritin test may be used to guide treatment^[16,17].

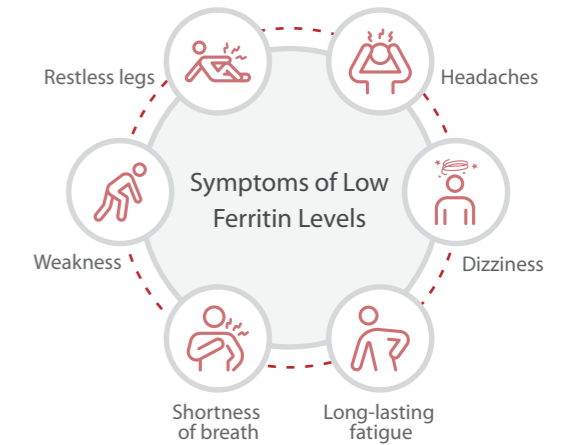


A ferritin blood test is a simple procedure to measure the levels of ferritin in the blood. It helps doctors to understand how much iron the body is storing, and to find out if the body has the right amount of iron to stay healthy. Too much or too little can cause serious health problems if it is untreated.

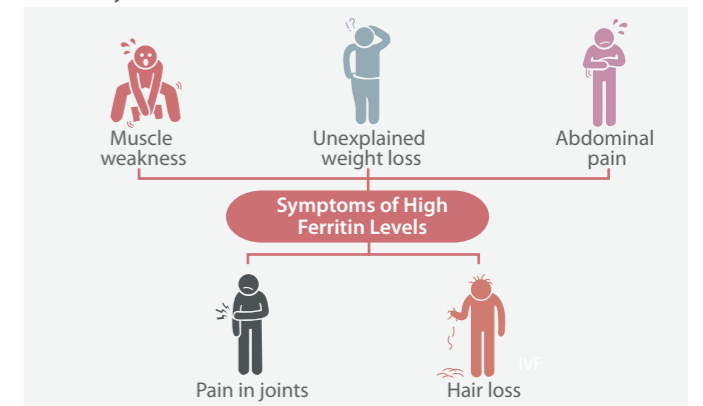


What might lead to a ferritin test?

If a ferritin test reveals that the blood ferritin level is lower than normal, it indicates that the body's iron stores are low, and that there is an iron deficiency. Without enough iron, a person could develop anemia.

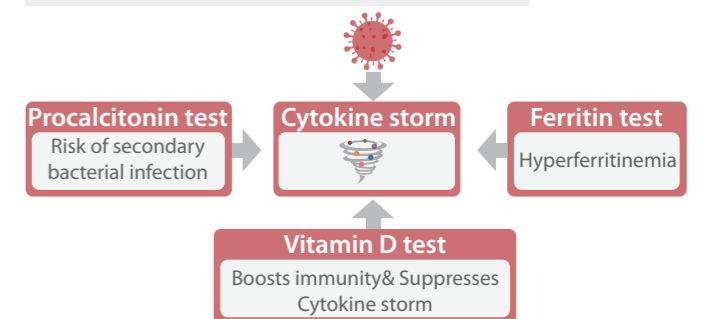


If the ferritin test reveals that the ferritin level is higher than normal, it may indicate that a condition is present that causes the body to store too much iron.

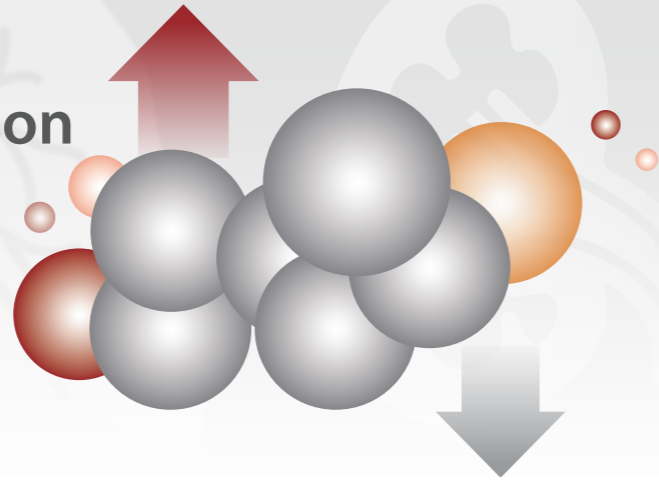


Based on these symptoms and other conditions, doctors may order a ferritin test for diagnostic and treatment guidance.

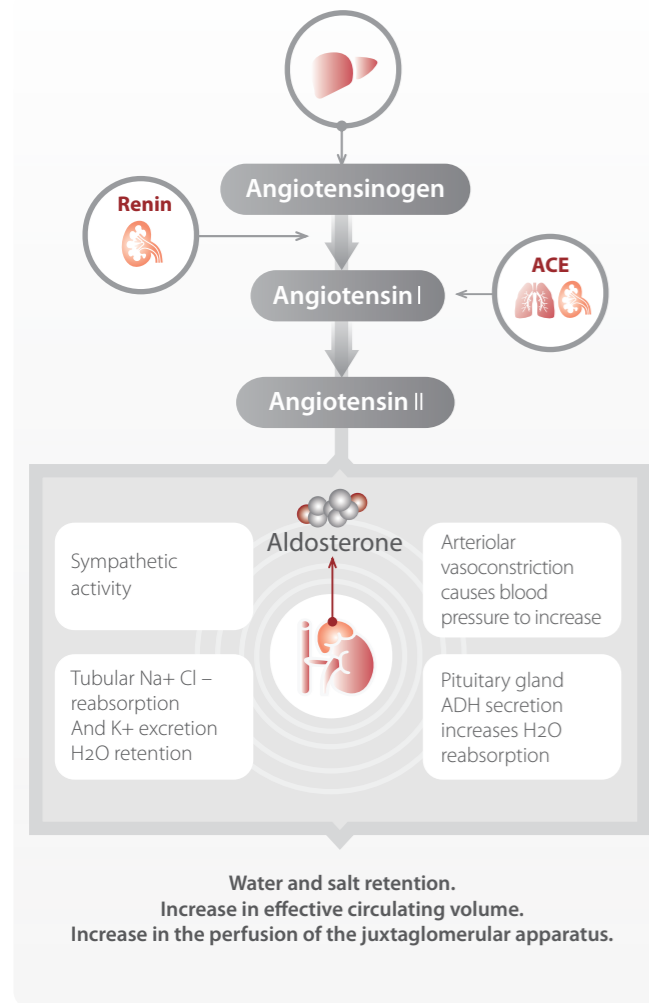
COVID-19 Correlated Biomarkers



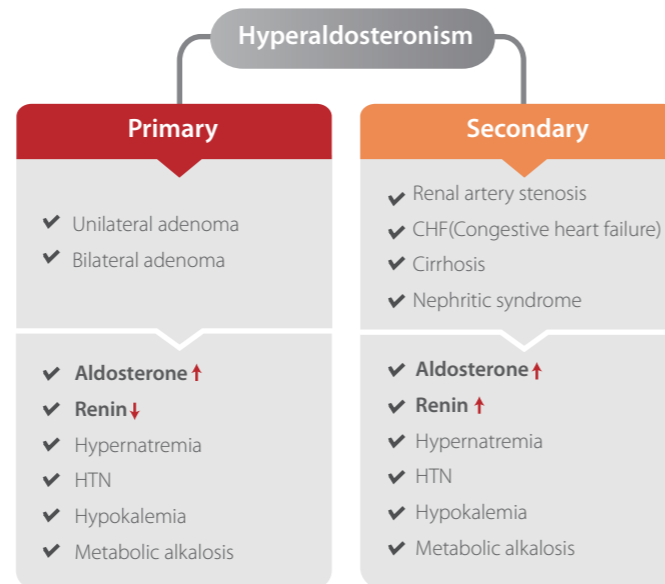
The Most Neglected Reason of Hypertension – The Role of Renin and Aldosterone in PA



Renin and Aldosterone in RAAS (Renin-Angiotensin-Aldosterone System)^[18]

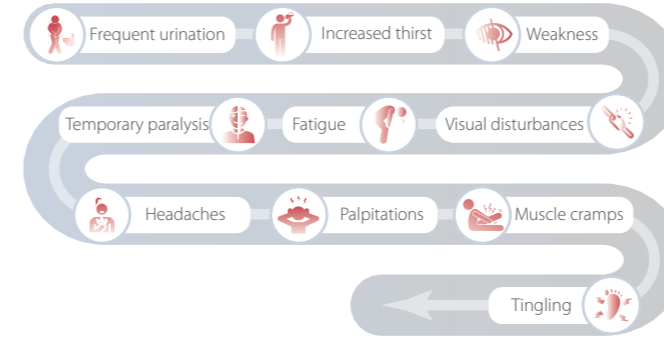


Different directions of renin and aldosterone in primary and secondary hyperaldosteronism^[19]



The syndrome of primary aldosteronism (PA) was first described by Conn in 1955. It is characterized by hypertension, suppressed plasma renin activity (PRA), increased plasma aldosterone concentration (PAC), and incompressible aldosterone levels in the blood or urine.

PA signs and symptoms are non-specific. These may include:



PA diagnosis is insufficient



All patients with hypertension should get tested^[20]

When to Consider Testing for Primary Aldosteronism:
All patients with hypertension should be tested at least once

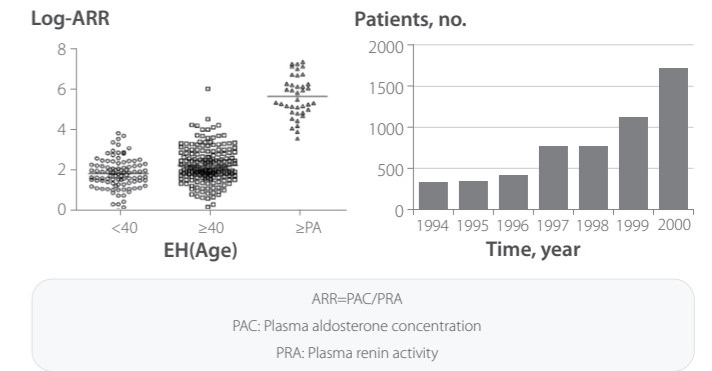
When to Consider Testing for Primary Aldosteronism:
Morning blood sample in seated ambulant patient
• Plasma aldosterone concentration (PAC)
• Plasma renin activity (PRA) or plasma renin concentration (PRC)

PAC ≥ 277 pmol/L (≥10 ng dL-1) and
↓ PRA (<1.0 ng mL-1h-1) or
↓ PRC (< lower limit of reference)

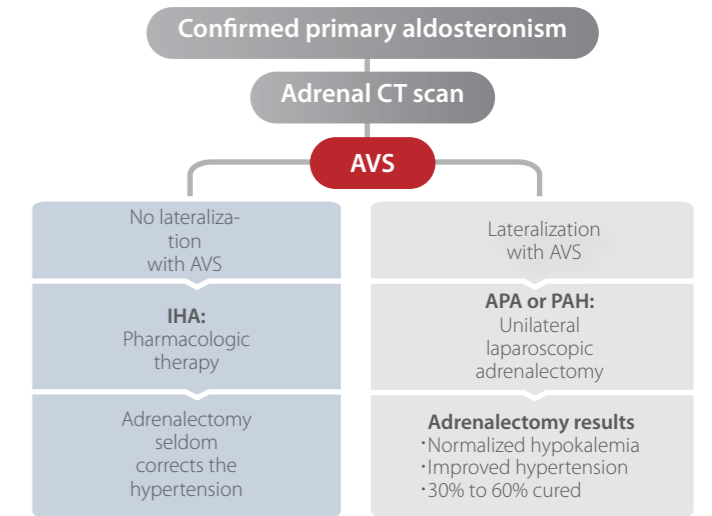
Confirmatory Testing (if spontaneous ↓ K+ absent):
• 24-h urine for aldosterone and sodium on a high sodium diet, or
• 4-h saline infusion test

ARR is a useful tool for PA detection

ARR screening leads to 10-fold increase in the annual detection rate of primary aldosteronism^[21].



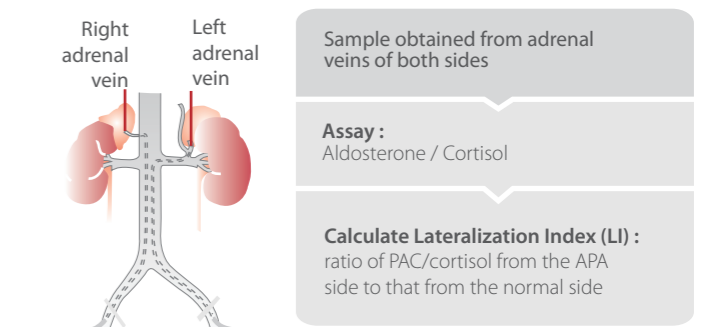
Distinguishing the subtype of primary aldosteronism is critical to deciding on the appropriate therapy



Subtyping algorithm

APA, aldosterone-producing adenoma;
AVS, adrenal venous sampling;
CT, computed tomography;
IHA, idiopathic hyperaldosteronism; PA, primary aldosteronism;
PAH, primary adrenal hyperplasia.

Due to the limitation of Computerized Tomography, adrenal venous sampling is needed^[22]

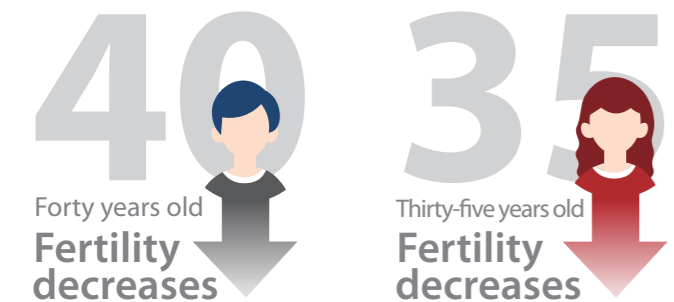
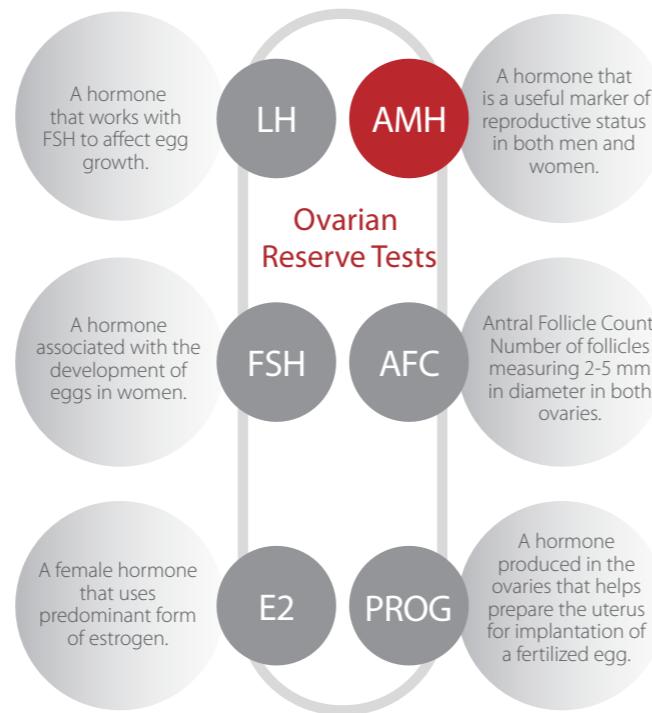




Struggling to get pregnant?

Age has a significant impact on fertility-fertility tends to drop after the age of 35 for women, and 40 for men.

For women who are preparing for pregnancy, it is advisable to check their ovarian reserve. Ovarian reserve is a term used to define the ovary's ability to provide viable egg cells for fertilization and consequently pregnancy. The ovarian reserve declines as women age, resulting in a decrease in the reproductive function^[23].



What hormones tests are frequently used to assess the ovarian reserve?

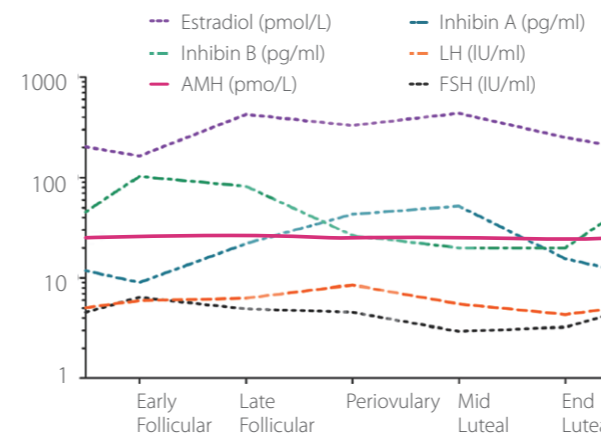
The ovarian reserve is a complex clinical phenomenon that is influenced by age, genetics, and environmental variables. The outcome can be predicted by performing ovarian reserve tests.

Why is AMH a better marker for the ovarian reserve?

AMH is produced by ovarian granulosa cells in women, and by Sertoli cells in the testis in men. Its first described function was in fetal sex differentiation.

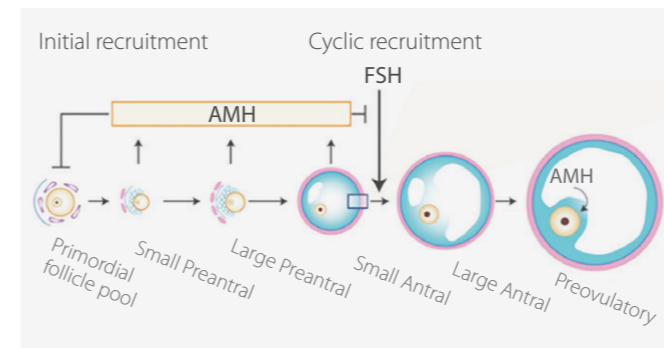
Estradiol, luteinizing hormone (LH) and follicle stimulating

hormone (FSH) levels change during the different phases of women's ovarian cycles. However, AMH levels remain constant^[24].



What is the role of AMH in the ovulation process?

The AMH value reflects the number of preantral follicles developed from the original follicle, which is the reserve function of the ovary^[26].



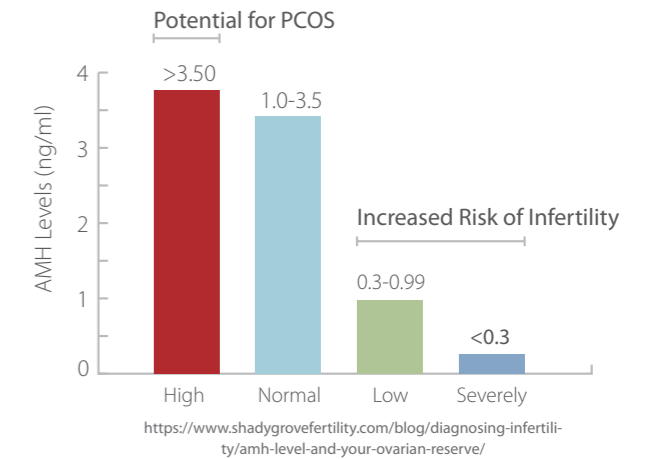
Do AMH levels change with age?

AMH is produced in the follicles of women of reproductive age and inhibits the transition of follicles from the primordial to the primary stage. AMH controls follicular maturation using two mechanisms and thereby controls the two different stages of follicular recruitment.

Age	ng/ml	pmol/L
Under 33 years old	2.1-6.8	15.0-48
33-37 years old	1.7-3.5	12.14-32.13
38-40 years old	1.1-3.0	7.8-21.42
41+ years old	0.5-2.5	3.57-17.85

<https://www.whitelotusclinic.ca/blog/dr-fiona-nd/amh-pcos-test/>

What are the factors that may affect serum AMH?^[27]



Increase AMH

- PCOS

No Influence

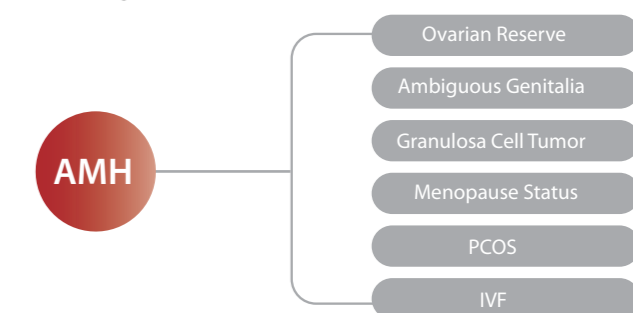
- Day of menstrual cycle
- Oral contraceptives
- GNRH agonists
- Pregnancy

Decrease AMH

- Increasing age
- Administration of gonadotropin
- Administration of chemotherapy or radiation
- Increased body mass index
- Oophorectomy

Why AMH is widely assessed in clinical settings?

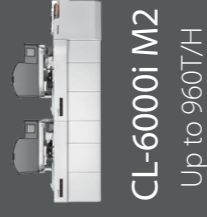
Serum AMH levels are indicative of the size of the growing follicle pool. Changes in serum AMH levels occur relatively early in the sequence of events associated with ovarian aging. AMH demonstrates the highest accuracy in predicting the occurrence of menopausal transition. Therefore, AMH is applied as a marker for ovarian status evaluations in many clinical settings^[28,29,30].



For small labs



For medium labs



Applicable for all labs
System Reliability
Stability
Efficiency
Traceability

CLIA Solution

Endocrinology

Adrenal Function

DHEA-S
Cortisol
ACTH

PA (Primary Aldosteronism)

Renin
Aldosterone

Growth Hormone

Growth Hormone*
IGF-1*

Cardiac

CK-MB
Myoglobin
Troponin I
BNP
NT-proBNP*
hs-TnI*

Metabolic

Diabetes

Insulin
C-peptide

Bone Metabolic

PTH
Calcitonin
Vitamin D total

Anemia

Ferritin
Vitamin B12
Folate
RBC Folate

Fertility

AMH

F-β-HCG*
PAPP-A*
FSH
Estradiol
Total β-HCG
TESTO
17-OH PROG*
LH
Free testosterone*

Thyroid

FT3
FT4
T3
T4
TSH

Anti-Tg

Anti-TPO
Tg
rT3
TRAb*

Female Cancer

CA125
HE4
CA15-3

Prostate Cancer

Free PSA
Total PSA

Gastrointestinal Cancer

CA19-9
CA242
CA72-4
PG I

Liver Cancer

AFP
AFP-L3%*
PIVKA-II*

Liver Fibrosis

Laminin
Hyaluronic Acid
PIIINP
Collagen IV

Lung Cancer

CEA
NSE
CYFRA 21-1
SCCA
ProGRP

Inflammation

PCT
IL-6*
Presepsin*

Toxco

Toxo IgG*
Toxo IgM*
Rubella IgG*
Rubella IgM*
CMV IgG*
CMV IgM*

ToRCH

CMV IgM*
HSV-1/2 IgG*
HSV-1/2 IgM*
HSV-1 IgG*
HSV-2 IgG*

Infectious Diseases

HIV Combo
HBSAg
Anti-HBs
HBeAg
Anti-HBe
Anti-HBc
Anti-HCV
Anti-TP (Syphilis)
HAV IgM*

Assay Menu

Tumor Marker

Prostate Cancer

Free PSA
Total PSA

Gastrointestinal Cancer

CA19-9
CA242
CA72-4
G-17*
PG I
Hp IgG*

Liver Cancer

AFP
AFP-L3%*
PIVKA-II*

Liver Fibrosis

Laminin
Hyaluronic Acid
PIIINP
Collagen IV

Lung Cancer

CEA
NSE
CYFRA 21-1
SCCA
ProGRP

Inflammation

PCT
IL-6*
Presepsin*

Toxco

Toxo IgG*
Toxo IgM*
Rubella IgG*
Rubella IgM*
CMV IgG*
CMV IgM*

ToRCH



CMV IgM*
HSV-1/2 IgG*
HSV-1/2 IgM*
HSV-1 IgG*
HSV-2 IgG*

Infectious Diseases



HIV Combo
HBSAg
Anti-HBs
HBeAg
Anti-HBe
Anti-HBc
Anti-HCV
Anti-TP (Syphilis)
HAV IgM*

*under development
Not all assays are available in every region




Mindray's Investments and Efforts in CLIA




Turku R&D Center

Wuhan R&D Center

Oakdale R&D Center

Shenzhen Guangming R&D Center
Shenzhen Headquarters

4 R&D centers for CLIA
Mindray spends 10% of its revenue on R&D
Over 3300 engineers, of whom over 69% hold Master degree or above
Over 6600 patent applications

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