



Internal Medicine Residency Spokane

Reference Deranged: “Normal” Labs that are Abnormal

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Introduction

- Plenty of numbers to keep track of in medicine, especially in primary care
- Defining normal vs abnormal values with regards to labs influences therapeutic management
- Reliance on electronic health record data and tools to establish normal vs abnormal
- **Four sets of lab values that are commonly reported as “normal”:**
 - Liver Enzymes
 - Iron Studies
 - Vitamin B12
 - Renal Function

Liver Enzymes (ALT and AST)

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Liver Enzymes (ALT and AST)

Liver chemistries, NOT liver function tests

- Enzymes responsible for amino group transfers
- ALT: specific to liver
- AST: present in tissues outside of the liver too

Author /Year	Proposed ALT ULN (male)	Proposed ALT ULN (female)	Comments
Neuschwander-Tetri <i>et al.</i> (13)	40IU/l	40IU/l	Gender not specified, not derived from data
Piton <i>et al.</i> (18)	42 IU/l for males with BMI≤23 and 66 IU/l if BMI>23	31 IU/l for females with BMI≤23 and 44 IU/l if BMI>23	Derived from reference population with HCV
Prati <i>et al.</i> (24)	30IU/l	19IU/l	Derived from reference population
Lee <i>et al.</i> (25)	33IU/l	25IU/l	All had normal liver biopsies
Ruhl and Everhart (26)	29IU/l	22IU/l	Derived from NHANES
Wright <i>et al.</i> (34)	33IU/l	–	Gender not specified

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ULN, upper limit of normal.

Liver Enzymes (ALT and AST)

AJG Summary: normal ALT range: 29-33 IU/l for males, 19-25 IU/l for females

- **Normal ALT does not exclude liver disease**
- Wide variability in reference range due to differences in healthy control population
- Linear relationship between ALT and BMI

Providence EPIC Reference Ranges

- ALT: 17-63
- AST: 10-45
- The upper limit of normal (ULN) in electronic medical records (EMR) can be abnormal

Primary Care Significance

- There is a broad differential for mild transaminitis but the non-alcoholic fatty liver disease (NAFLD) is the most common cause in developed countries
- Trusting the EMR reference range likely could lead to missed cases of NAFLD and other liver pathology

Liver Enzymes (ALT and AST)

❖ Relevance: increasing evidence that elevated liver enzymes are associated with morbidity and mortality

Author /year	Proposed ALT/AST cutoff level	ALT/AST level for increased mortality	Comments
Arndt <i>et al.</i> (27)	AST 18	AST>18	3X increase in all cause mortality
Kim <i>et al.</i> (28)	ALT<20	ALT 30–39	RR of liver mortality 2.9 (2.4–3.5) and 9.5 (7.9–11.5) in men, 3.8 (1.9–7.7) and 6.6 (1.5–25.6) in women
Lee <i>et al.</i> (29)	ALT (ULN 45 IU/l for M, 29 for F)	ALT 45–90 M 29–58 for F	SMR risk 1.32 for 1–2X ULN, and 1.78 for >2X ULN
Ruhl and Everhart (30)	ALT 30 IU/l M, 19 IUL for F	ALT>30 for M ALT >19 for F	Increased liver related mortality

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; RR, relative risk; M, male; ULN, upper limit of normal.

Liver Enzymes (ALT)

If we lowered the ULN for ALT, how would that alter clinical practice?

Pros

- Diagnose more liver disease: significant liver disease can occur in setting of normal liver enzymes

Cons

- Increased health care costs
- Unnecessary evaluations
- Lowering blood donor pool



Ferritin

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Ferritin "normal" values vary highly

Component	Ref Range & Units
 FERRITIN	11 - 307 ng/mL

Epic reference interval (adult female >15 y/o)

FERRITIN, P/S	MALE, FEMALE UNKNOWN µg/L
	0 – <6 mo 50-500
	6mo – 15 yrs 15 – 100
	FEMALE
	>15 yrs 20-300
	MALE, UNKNOWN
	>15 yr 30 – 500

Meditech reference interval

Age	Male (ng/mL)	Female (ng/mL)
0 to 5 m	13-273	12-219
6 to 12 m	12-95	12-110
1 to 5 y	12-64	12-71
6 to 11 y	16-77	15-79
12 to 19 y	16-124	15-77
Adult	30-400	15-150

Labcorp reference intervals

Test Details

Methodology

Immunoassay (IA)

Reference Range(s)

Pediatric

<4 Days	Not established
4-14 Days	100-717 ng/mL
15 Days-5 Months	14-647 ng/mL
6-11 Months	8-182 ng/mL

Male

1-4 Years	5-100 ng/mL
5-13 Years	14-79 ng/mL
14-15 Years	13-83 ng/mL
16-18 Years	11-172 ng/mL
19-59 Years	38-380 ng/mL
>59 Years	24-380 ng/mL

Female

1-4 Years	5-100 ng/mL
5-13 Years	14-79 ng/mL
14-18 Years	6-67 ng/mL
19-40 Years	16-154 ng/mL
41-60 Years	16-232 ng/mL
>60 Years	16-288 ng/mL

Quest Diagnostics reference intervals

What is considered a "low ferritin"?

- Serum ferritin is the most frequently ordered test to diagnose iron deficiency, however proposed cut-off values generally range from 15-100ng/mL.
- Highly variable dependent on which laboratory or EMR is being used to interpret values.
- Also depends on patient's past medical history (HF, CKD)
- Different associations/organizations have different cut offs dependent on a patient's risk factors and active medical problems.

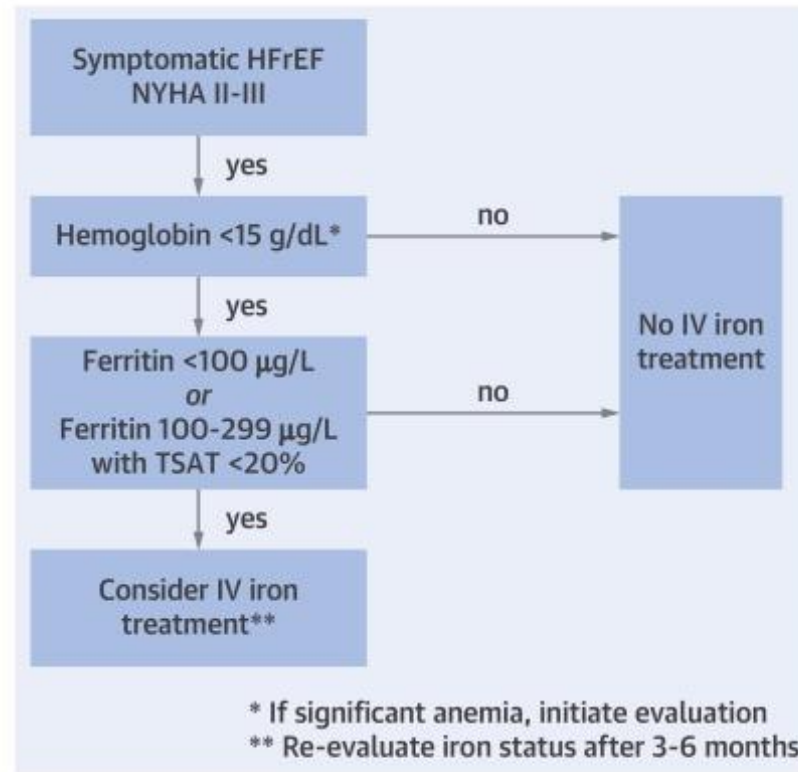
Iron Deficiency Anemia – American Gastroenterological Association (AGA)

- In patients with anemia (Hgb<13 in males, <12 in females), the AGA recommends using a **ferritin cutoff of 45ng/mL** when using ferritin to diagnose iron deficiency (1) in the general population.

Using Ferritin to diagnose Iron Deficiency in HFrEF

- All patient's with HFrEF should be screened and treated for iron deficiency anemia if present.
- Diagnosis of IDA in patients with HFrEF: (1,2)
 - **Ferritin <100**
OR
 - **Ferritin <300 + Tsat <20%**
- No data currently exists for treatment of IDA in HFpEF, though clinical trials are currently ongoing (FAIR-HFpEF).
- Primary care significance
 - Iron deficiency affects up to 50% of patients with heart failure with reduced ejection fraction and is associated with poorer exercise capacity, and increased risk of mortality.

CENTRAL ILLUSTRATION: Diagnostic Algorithm for Treatment of Iron Deficiency in Patients With HF According to ESC Guidelines and Expert Consensus Recommendations



von Haehling, S. et al. J Am Coll Cardiol HF. 2019;7(1):36-46.

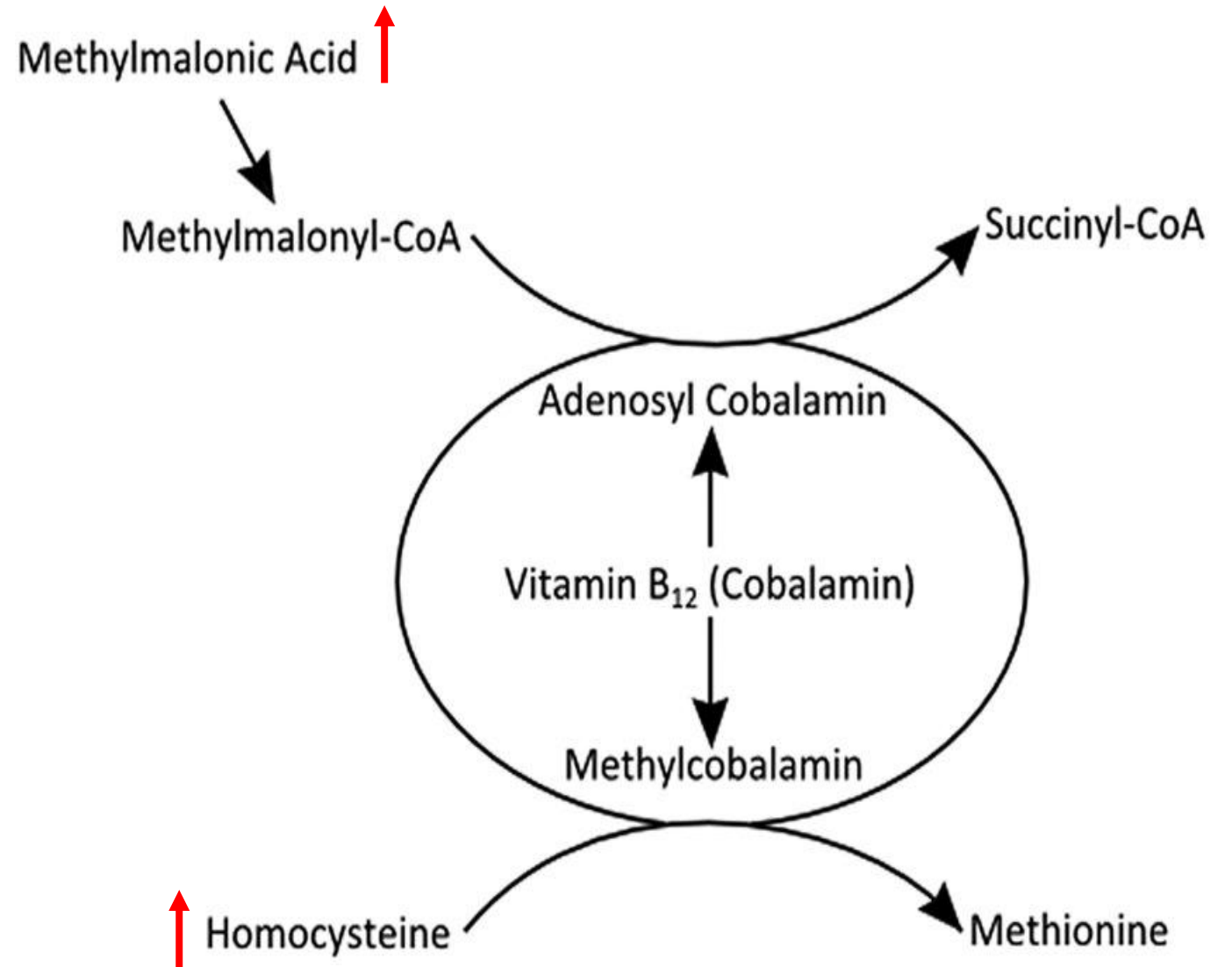
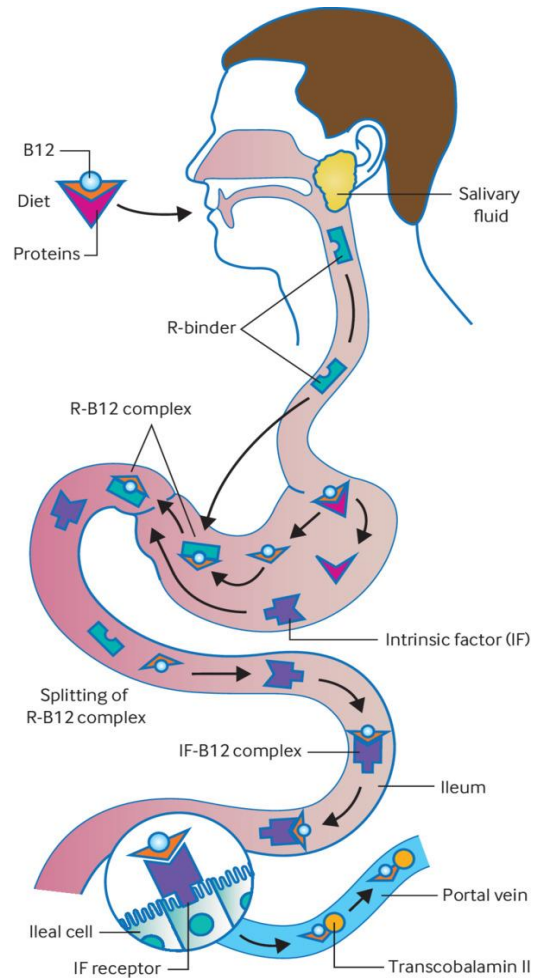
Using Ferritin to diagnose Iron Deficiency in Chronic Kidney Disease

- Anemia in patients Chronic Kidney Disease is associated with an increase in mortality and hospitalizations (1).
- Hemoglobin should be monitored periodically in patients with CKD
 - CKD 3: at least annually
 - CKD 4: at least every 6 months
 - CKD 5: at least every 3-6 months
- Anemia is diagnosed in patients with CKD with:
 - Hemoglobin <13g/dL in males
 - Hemoglobin <12g/dL in females
- If an increase in Hg is desired, iron should be repleted in patients with CKD via PO or IV when:
 - **Tsat <30% AND ferritin <500ng/mL**

Vitamin B12 Deficiency

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Vitamin B12



(Sukumar & Saravanan, 2019);

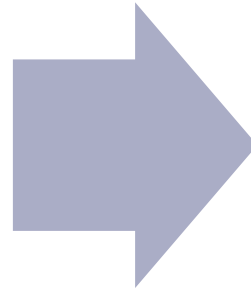
(Ankar & Kumar, 2022);

https://www.researchgate.net/figure/Figure2-Vitamin-B12-cobalamin-is-a-cofactor-in-conversion-of-methylmalonyl-coenzyme-A_fig1_276357092

Vitamin B12

Causes of Deficiency

- Celiac Disease
- Medications
- Pernicious anemia
- Veganism, etc



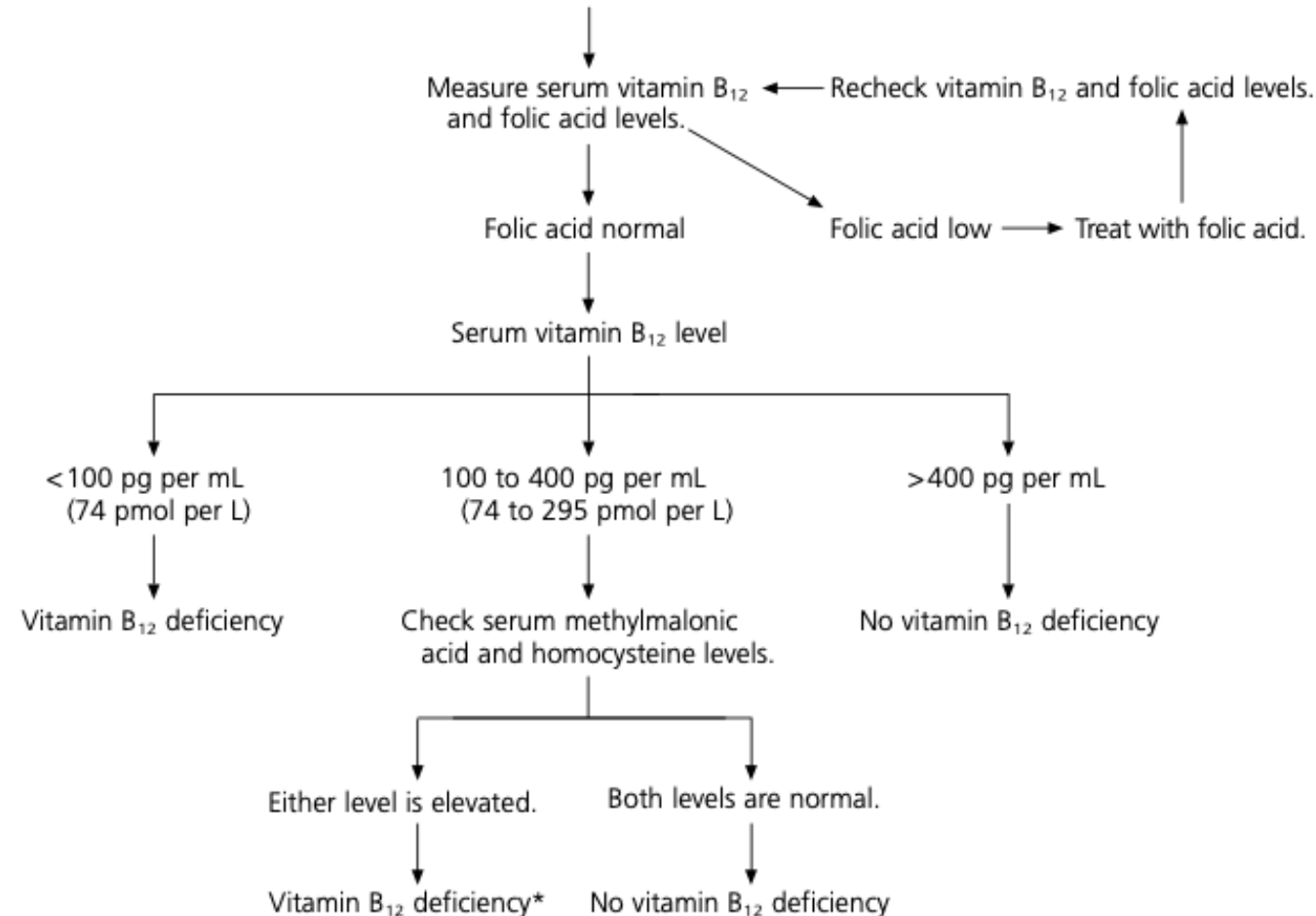
Symptoms

- Paresthesia in hands and feet
- Muscle cramps
- Dizziness
- Cognitive disturbance/Dementia/Psychosis, etc

Vitamin B12


Suspected Vitamin B₁₂ Deficiency

Hematologic, neurologic, or psychiatric abnormalities
Gastric or ileal surgery
Prolonged use of histamine H₂-receptor blockers or proton pump inhibitors
Chronic gastrointestinal symptoms
Age >65 years



(Robert & Brown, 2003)

Vitamin B12

Component		Ref Range & Units	1 mo ago (8/8/22)	1 yr ago (11/6/20)
	VITAMIN B-12	180 - 914 pg/mL	381	117 ▼ CM
Comment: Deficient: <211 pg/mL				
Borderline: >=211 - 246 pg/mL				
Resulting Agency			PMGPMP	PMGSPOK CERNER

Component		Ref Range & Units	1 mo ago
	METHYLMALONIC ACID	0 - 378 nmol/L	514 ^
Resulting Agency			LabCorpSD

Vitamin B12

Overview:

- Many causes
- Question the reference range
- Consider measuring an MMA in conjunction with vitamin B12 +/- homocysteine level
- May consider trial of injections vs * oral therapy

*oral therapy in high doses effective

Vitamin B12

Overdose of
vitamin
B12?

Elevated
levels?



<https://perniciousanemia.org/b12/toxicity/>



Creatinine

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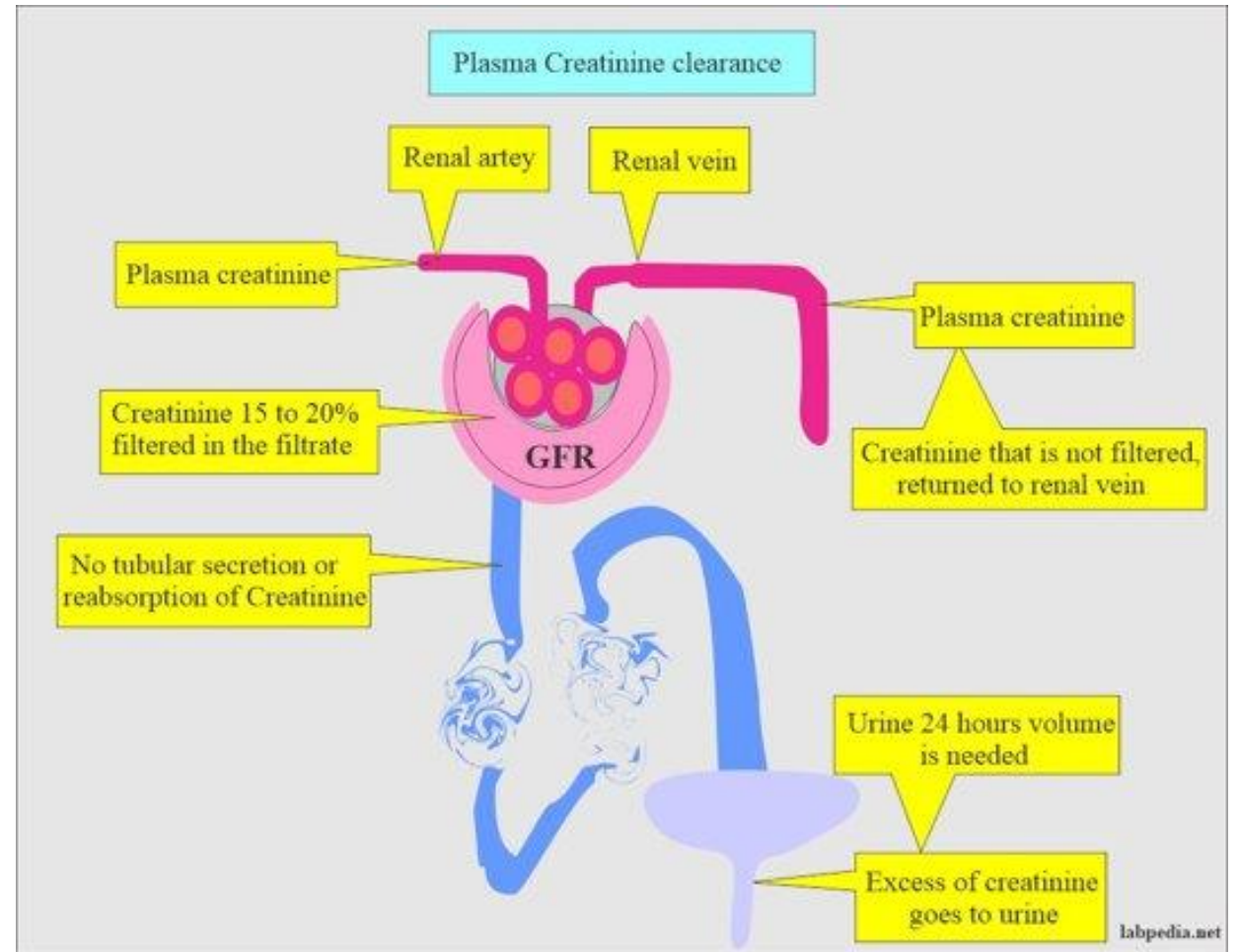
Normal Creatinine

Reference Range:

	Female	Male
≥ 15 y	0.57–1.00	0.76–1.27

Factors That Affect Normal Creatinine

- Muscle mass
- Intake (protein rich foods)
- Tubular Filtration



But Why Is It Low?

- Malnutrition
- Low BMI/muscle mass
- Quadriplegia
- Amputations
- Cirrhosis
- Vegetarian diet
- Neuromuscular disorders
- **Low can be normal IF it is stable**

For Example: 61y F w/ DM2, frail s/p R AKA

Na	136 - 144 mmol/L	135 ▼
K	3.6 - 5.3 mmol/L	3.8
Cl	101 - 111 mmol/L	99 ▼
CO2	22 - 32 mmol/L	27
Anion Gap	5 - 16 mmol/L	9
Glucose	74 - 100 mg/dL	362 ▲
Comment: Males and females for random glucose result: >200		
BUN	8 - 20 mg/dL	17
Creatinine	0.50 - 1.00 mg/dL	0.60

For Example: 61y F w/ DM2, frail w/ RLE AKA

How About Now?

Na	136 - 144 mmol/L	135 ▼	143 ^R	141 ^R
K	3.6 - 5.3 mmol/L	3.8	3.6 ^R	2.9 ▼ ^R
Cl	101 - 111 mmol/L	99 ▼	105 ^R	103 ^R
CO2	22 - 32 mmol/L	27	27 ^R	25 ^R
Anion Gap	5 - 16 mmol/L	9	11	13
Glucose	74 - 100 mg/dL	362 ▲	266 ▲ ^R	248 ▲ ^R
omment: Males and females for random glucose result: >200 mg/dL diagnostic of diabetes if hypergl				
BUN	8 - 20 mg/dL	17	13 ^R	12 ^R
Creatinine	0.50 - 1.00 mg/dL	0.60	0.33 ▼ ^R	0.32 ▼ ^R
Calcium	8.9 - 10.3 mg/dL	9.5	8.8 ^R	8.6 ^R

GFR and Albuminuria

- Microalbumin can be helpful for risk stratification

				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (mL/min/1.73 m ²) description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60-89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

Confirming GFR

Serum Cystatin C

Inulin (very expensive)

Iohexol or EDTA

24 hour Cr Cl

Serum Cystatin

- 2021 CKD-EPI creatinine-cystatin C equation
 - Require info: Age, serum Cr and serum cystatin
 - More specific when estimating GFR < 60
 - Less variation between gender and race
 - Less association with body mass

24-hr Cr Clearance

- Limited by accuracy of urine collection
- Cumbersome to preform

Box 1

Settings in which creatinine-based eGFR should be confirmed:

- Factors present that affect endogenous sources of creatinine:
 - Very high muscle mass
 - Very low muscle mass (eg, chronic heart failure, amputations, neuromuscular disease)
 - Advanced liver disease
- Factors present that affect exogenous sources of creatinine:
 - Very high animal protein diet
 - Very low-protein diet (eg, vegetarian, vegan)
- In patients with creatinine based-eGFR 45 to 59 mL/min/1.73 m² and no other evidence of kidney disease (eg, no albuminuria or radiologic abnormality)
- In settings where accuracy of the GFR estimate is more important:
 - Potential kidney donors
 - When treatment is planned with a medication that is renally cleared, has significant toxicity, and a narrow therapeutic range (eg, some chemotherapy agents)

Key Points

Liver Enzymes

- Normal ALT range: 29-33 IU/l for males, 19-25 IU/l for females
- Normal ALT does not exclude liver disease

Ferritin

- Ferritin cutoff of 45 ng/mL in general population
- HFrEF: Ferritin <100 OR Ferritin <300 + Tsat <20%
- CKD: Tsat <30% AND ferritin <500 ng/mL

Key Points

Creatinine

- Pay attention to Cr trend rather than individual value
- Consider cystatin to confirm GFR when in doubt

Vitamin B12

- Borderline levels require further evaluation with MMA +/- homocysteine
- High levels might indicate systemic disease but do not indicate need to stop
- Can present unexpectedly (depression, fatigue, erectile dysfunction)

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