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Symptoms

Fatigue

Restless legs syndrome

Headache

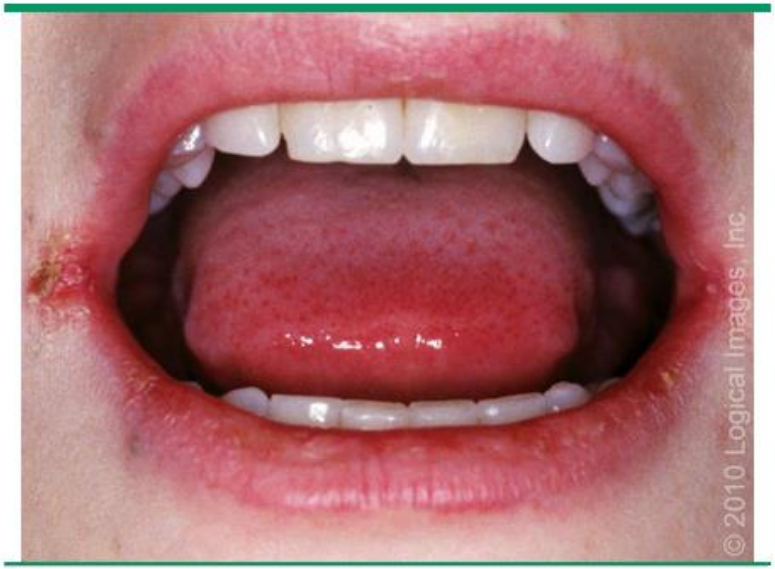
Exercise intolerance

Exertional dyspnea

Weakness

Physical Examination

Angular cheilitis



Erythema and fissures are present at the corners of the mouth.

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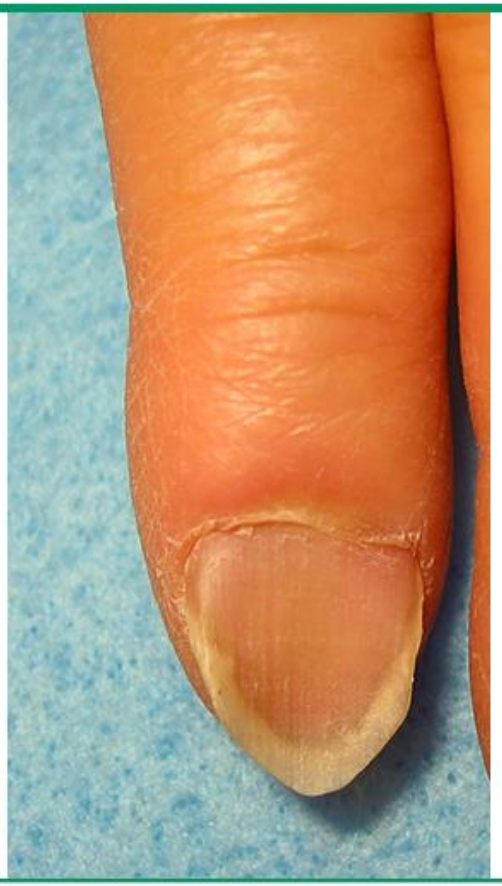
Koilonychia (spoon nail)



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What should you ask for a detailed Medical History?

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Laboratuary findings

TAM KAN SAYIMI

LÖKOSİT (WBC)	7,14	x10^9/L	4,5 - 11	5.98 25.02.2020	7.49 28.08.2019
ERİTROSİT (RBC)	3,92	x10^12/L	3,8 - 5,1	4.43 25.02.2020	4.65 28.08.2019
TROMBOSİT (PLT)	462 *	x10^9/L	150 - 400	400 25.02.2020	388 28.08.2019
HEMOGLOBİN (Hb)	* 7,8	g/dL	11,7 - 15,5	10.3 25.02.2020	12.2 28.08.2019
HEMATOKRIT (%)	* 26,4	%	35 - 45	34.9 25.02.2020	38.9 28.08.2019
ORTALAMA ERITROSIT HACMİ (MCV)	* 67,3	fL	81 - 100	78.8 25.02.2020	83.7 28.08.2019
ORTALAMA ERITROSIT HEMOGLOBINI (MCH)	* 19,9	pg/cell	27 - 34	23.3 25.02.2020	26.2 28.08.2019
ORTALAMA ERITROSIT HEMOGLOBİN KONS.(MCHC)	* 29,5	g/dL	32 - 36	29.5 25.02.2020	31.4 28.08.2019
ERİTROSİT DAĞILIM GENİŞLİĞİ (RDW)	18,9 *	%	11,5 - 14,5	16.0 25.02.2020	14.9 28.08.2019
NÖTROFIL %	55,6	%	40 - 70	50.4 25.02.2020	50.9 28.08.2019
LENFOSIT %	34,0	%	20 - 45	38.8 25.02.2020	37.8 28.08.2019
MONOSIT %	8,7	%	3 - 9	8.4 25.02.2020	8.8 28.08.2019
EOZINOFIL %	1,1	%	0 - 6	1.7 25.02.2020	2.0 28.08.2019
BAZOFIL %	0,6	%	0 - 1	0.7 25.02.2020	0.5 28.08.2019
NÖTROFIL SAYISI	4,97	x10^9/L	1,8 - 7,7	3.02	3.81

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SERUM DEMİRİ VE TOTAL DEMİR

UIBC	440 *	µg/dL	135 - 392	412 25.02.2020	403 28.08.20
%SATURASYON (Transferrin Saturasyonu)	* 4	%	13 - 45	5 25.02.2020	13 28.08.20
TOTAL DEMİR BAĞLAMA KAPASİTESİ	457 *	µg/dL	250 - 450	435 25.02.2020	461 28.08.20
	81,8	µmol/L	44,75 - 80,55		
SERUM DEMİRİ	* 17	µg/dL	37 - 145	23 25.02.2020	58 28.08.20

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Hormon Metabolik CEBECİ HASTANESİ MERKEZ LABORATUVARI

Örnek Türü :SERUM

FERRİTİN	* 2,0	ng/mL	13 - 150	2.1 25.02.2020	4.2 28.08.20
B12 VİTAMİNİ	525	pg/mL	197 - 771	439 17.06.2021	319 25.02.20
FOLİK ASİT	8,11	ng/mL	3,89 - 20	13.75 25.02.2020	8.15 28.08.20

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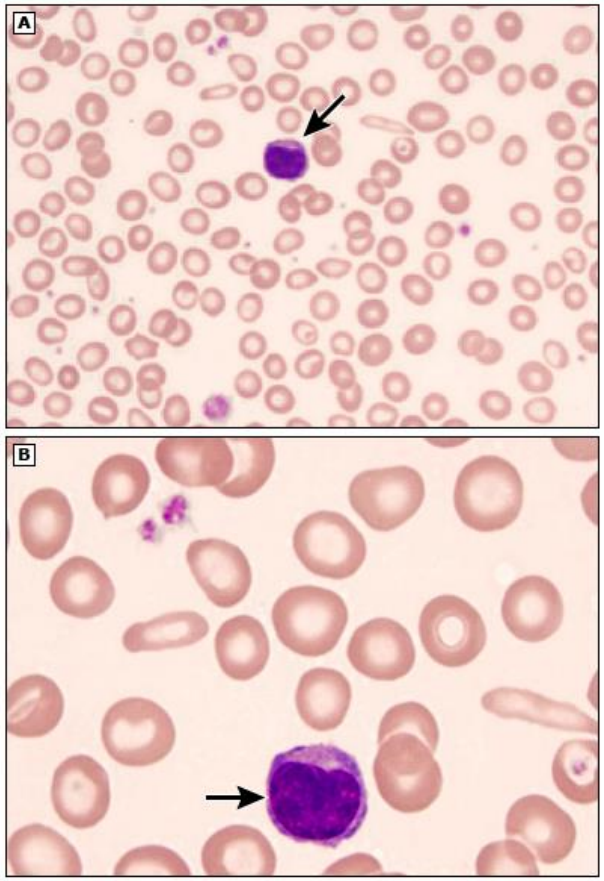
Peripheral blood smear in iron deficiency anemia showing microcytic, hypochromic red blood cells



The same peripheral blood smear from a patient with iron deficiency is shown at two different magnifications. Small (microcytic) red blood cells are shown, many of which have a thin rim of pink hemoglobin (hypochromia). Occasional "pencil"-shaped cells are also present. A small lymphocyte is shown for size comparison (arrow). Normal red blood cells are similar in size to the nucleus of a small lymphocyte (arrow), and central pallor in normal red blood cells should equal approximately one-third of the cell diameter.

Kindly supplied by Dr. German Pihan, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

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What is the diagnosis?

What are the causes of anemia?

Causes of anemia in adults

RBC size/ MCV	Reticulocyte count	
	Low or normal*	Increased
Microcytic MCV <80 fL	▪ Iron deficiency (late) ▪ Anemia of chronic disease/inflammation ▪ Sideroblastic anemias	▪ Thalassemia ▪ Hemolysis¶
Normocytic MCV 80 to 100 fL	▪ Bleeding (acute) ▪ Iron deficiency (early) ▪ Anemia of chronic disease/inflammation ▪ Bone marrow suppression (cancer, aplastic anemia, infection) ▪ Chronic renal insufficiency ▪ Hypothyroidism ▪ Hypopituitarism ▪ Excess alcohol ▪ Copper deficiency/zinc poisoning	▪ Bleeding (with bone marrow recovery) ▪ Hemolysis¶ ▪ Bone marrow recovery (eg, after infection, vitamin B12 or folate replacement, and/or iron replacement)
Macrocytic MCV >100 fL	▪ Vitamin B12 or folate deficiency ▪ Excess alcohol ▪ Myelodysplastic syndrome ▪ Liver disease ▪ Hypothyroidism ▪ HIV infection ▪ Medications that interfere with nuclear maturation (hydroxyurea, methotrexate, some chemotherapy agents)	▪ Hemolysis¶ ▪ Bone marrow recovery (eg, after infection, vitamin B12 or folate replacement, and/or iron replacement)

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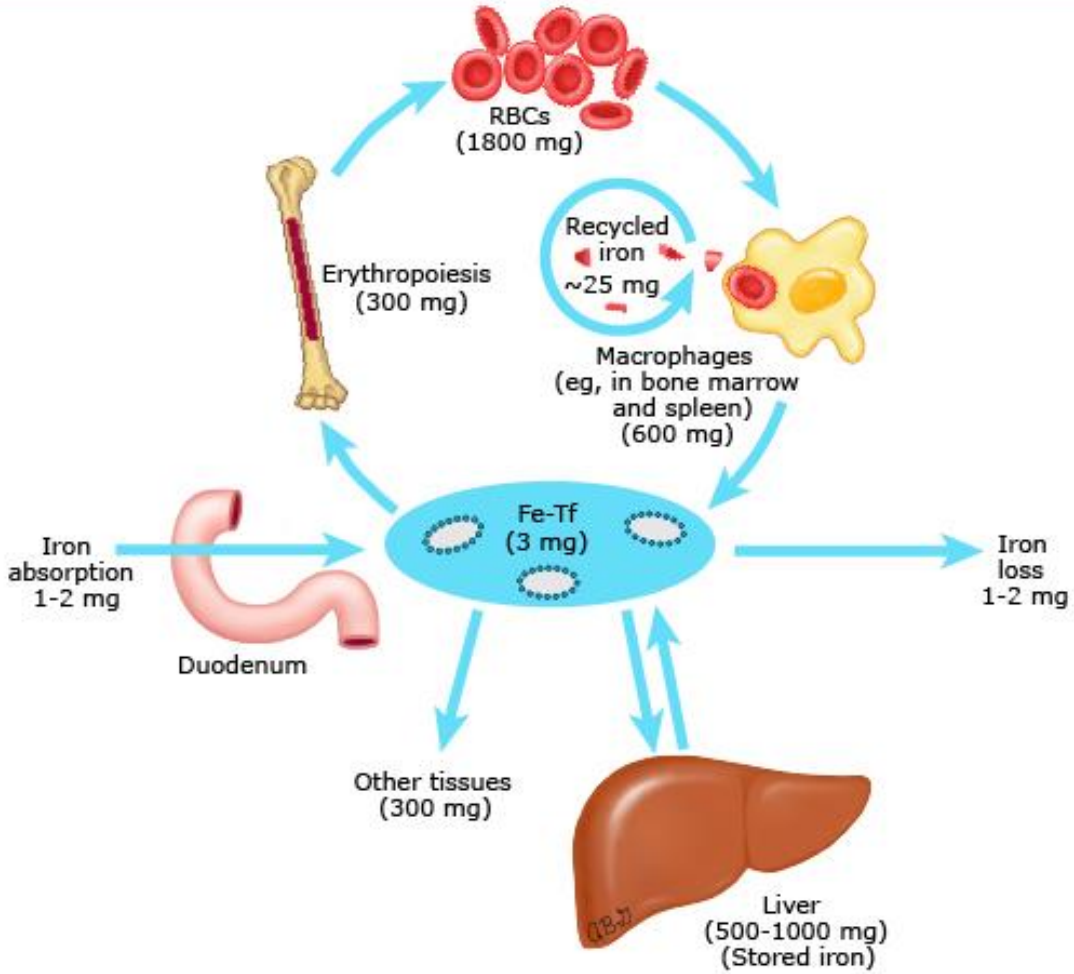
Regulation of iron absorption, transport, and homeostasis



Schematic showing iron homeostasis. Refer to UpToDate for details of the regulation of iron absorption, transport, and storage in the body.

RBCs: red blood cells; Fe-Tf: transferrin-bound iron, the major transport form in the body.

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Factors influencing the absorption and bioavailability of dietary iron

Absorption of heme iron
Amount of heme iron, especially in meat
Content of calcium in the meal (calcium impairs iron absorption)
Absorption of nonheme iron
Iron status
Amount of potentially available nonheme iron
Balance between positive and negative factors
Positive factors
Meat or fish (factors in meat other than heme iron enhance absorption of nonheme iron)
Negative factors
Phytate (in bran, oats, rye fiber)
Polyphenols (in tea, some vegetables and cereals)
Dietary calcium
Soy protein

Refer to UpToDate for additional discussions of approaches to improving iron absorption and use of intravenous iron as an alternative to oral iron.

Adapted from: Hallberg L, Rossander-Hulten L, Burne M. Nutritional anemias. In: Nestle Workshop Series, vol 30, Fomon SJ, Zlotkin S (Eds), Vevey/Raven Press, New York 1992. p.170.

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Iron Deficiency Anemia does not develop suddenly!

Laboratory findings during the development of iron deficiency

	Normal	Iron deficiency without anemia	Iron deficiency with mild anemia	Severe iron deficiency with severe anemia
Hemoglobin	Normal range*	Normal range*	**9 to 12 g/dL (90 to 120 g/L)**	**6 to 7 g/dL (60 to 70 g/L)**
Red blood cell size and appearance	Normal	Normal	**Normal or slight hypochromia (slight decrease in MCHC)**	**Microcytosis (decrease in MCV) and hypochromia (decrease in MCHC)**
Serum ferritin	40 to 200 ng/mL (40 to 200 mcg/L; 89.9 to 449 picoM/L)	**<40 ng/mL¶ (<40 mcg/L; <89.9 picoM/L)**	**<20 ng/mL (<20 mcg/L; <45 picoM/L)**	**<10 ng/mL (<10 mcg/L; <22.5 picoM/L)**
Serum iron	60 to 150 mcg/dL (10.7 to 26.7 microM/L)	60 to 150 mcg/dL (10.7 to 26.7 microM/L)	**<60 mcg/dL (<10.7 microM/L)**	**<40 mcg/dL (<7.1 microM/L**
Total iron-binding capacity (TIBC; transferrin)	300 to 360 mcg/dL (53.7 to 64.4 microM/L)	300 to 390 mcg/dL (53.7 to 69.8 microM/L)	**350 to 400 mcg/dL (62.6 to 71.6 microM/L)**	**>410 mcg/dL (>73.4 microM/L)**
Transferrin saturation (serum iron/TIBC)	20 to 50%	20%	**<15%**	**<10%**
Reticulocyte hemoglobin[1]	30.6 to 35.4 pg	22.3 to 34.7 pg	14.8 to 34.0 pg	Data not available
Bone marrow iron stain	Adequate iron present	**Iron absent**	**Iron absent**	**Iron absent**
Erythrocyte zinc protoporphyrin, ng/mL RBC	30 to 70	30 to 70	**>100**	**100 to 200**

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Algorithm for evaluating suspected iron deficiency

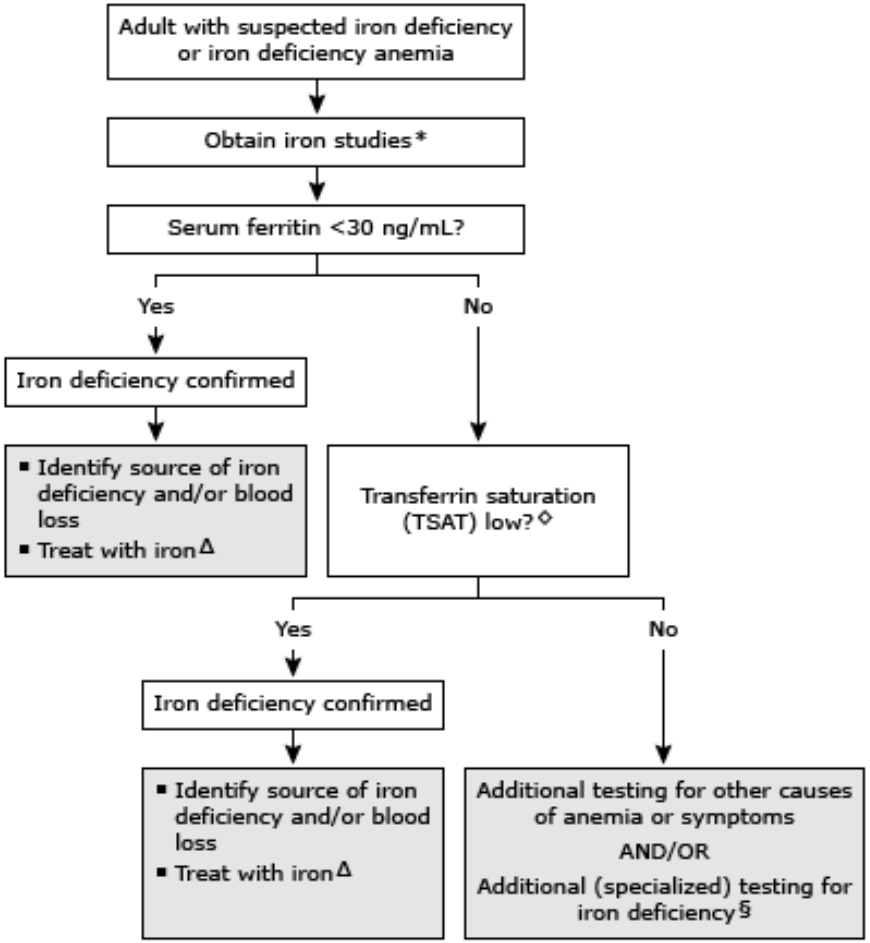
Findings in iron deficiency (selected examples)

History:
- Symptoms of anemia such as undue fatigue
- Pica, pagophagia (ice craving)
- Restless legs syndrome
- Celiac disease
- Heavy menses or prior pregnancies
- GI bleeding or frequent blood donation

Examination:
- Pallor, brittle skin
- Fingernail changes (spoon shape, horizontal lines)
- Cheilosis, loss of tongue papillae
- Occult blood in stool ¶

CBC:
- Anemia, low RBC count, low reticulocyte count
- Microcytic RBCs (low MCV); may be normocytic
- High platelet count

Iron studies panel
- Iron
- Transferrin or TIBC
- Ferritin
- Transferrin saturation (TSAT = iron/TIBC × 100)



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PO versus IV iron therapy

Gold standart is po iron replacement!!

Advantages and disadvantages of oral versus IV iron

	Advantages	Disadvantages
Oral iron	▪ Effective for most patients ▪ Extremely low risk of serious adverse events ▪ Initial costs very low	▪ Gastrointestinal side effects are common ▪ Compliance may be low ▪ May be inadequate for severe or ongoing blood loss ▪ May require administration for several months ▪ Total costs may be higher
IV iron	▪ Effective for most patients ▪ More rapid correction of anemia and resolution of symptoms ▪ Ability to administer large doses (up to 1000 mg elemental iron) in a single infusion ▪ Compliance is assured ▪ No gastrointestinal side effects	▪ Requires monitored intravenous infusion ▪ Rare cases of allergic or infusion reactions ▪ Requires equipment and personnel to treat allergic or infusion reactions ▪ Initial costs may be higher

Refer to UpToDate content on the management of iron deficiency for further details. Advantages, disadvantages, costs, and burdens for any individual patient may depend on a number of factors.

IV: intravenous.

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Oral iron products

Drug	Examples of United States trade (brand) names	Elemental iron content (mg iron per mg tablet or per mL liquid)*
Ferrous fumarate (Contains 33% elemental iron per mg of mineral salt)	▪ Tablets	
	Various over-the-counter and store-brand products with "iron" in the name	29.5 mg/90 mg
	Ferrimin 150	150 mg elemental iron per tablet
	Ferretts, Ferrocite, Hemocyte	106 mg/324 or 325 mg
Ferrous gluconate (Contains approximately 10 to 14% elemental iron per mg of mineral salt)	▪ Tablets	
	Fergon, Ferrotabs	27 mg/240 mg
	Various over-the-counter and store-brand products with "iron" in the name	28 mg/256 mg or 38 mg/324 or 325 mg
Ferric maltol (Contains 30 mg elemental iron complexed with 201.5 mg trimaltol per capsule)	▪ Capsules	
	Accrufer (requires a prescription)	30 mg elemental iron per capsule
Ferrous sulfate (Generally contains 20 to 30% elemental iron per mg of mineral salt but can vary by manufacturer)	▪ Liquids	Multiple concentrations exist; check packaging closely
	BProtected Pedia, Fer-In-Sol, Fer-Iron	15 mg/1 mL ("drops," "solution")
	FeroSul	44 mg/5 mL ("elixir," "liquid")
	Various over-the-counter and store-brand products with "iron" in the name	60 mg/5 mL ("syrup")
	▪ Tablets	
	Feosol original	65 mg/200 mg
	Ferro-Bob, FerrouSul	65 mg/325 mg
Polysaccharide-iron complex (PIC) (Also available as PIC plus folic acid and PIC plus folic acid and vitamin B12)	▪ Liquids	
	NovaFerrum	15 mg/1 mL ("drops")
	NovaFerrum 125	125 mg/5 mL ("liquid")
	▪ Capsules	
	EZFE 200, Ferrex 150, Ferric-X 150, iFerex 150, Myferon 150, NovaFerrum 50, Nu-Iron 150, PIC 200, Poly-Iron 150	The number in the name is the mg of elemental iron (eg, NovaFerrum 50 contains 50 mg elemental iron per capsule)

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Intravenous iron products (use in adults)

Drug	Trade (brand) name	Concentration of elemental iron	Dosing (adults)	Test dose*	Premedication
Ferric carboxymaltose (FCM)	Injectafer (United States), Ferinject (United Kingdom and other countries)	50 mg/mL	▪ Weight ≥50 kg: 1 or 2 doses of 750 mg, given 7 or more days apart **-OR-** ▪ Weight <50 kg: 1 or 2 doses of 15 mg/kg, given 7 or more days apart	Not required	▪ We do not routinely premedicate for any of the IV iron products. ▪ For patients with asthma, multiple drug allergies, or inflammatory arthritis, we often give methylprednisolone alone prior to the iron infusion. We do not give diphenhydramine.
Ferric gluconate (FG)	Ferrlecit	12.5 mg/mL	▪ Multiple doses of 125 to 250 mg	Not required, but recommended if the patient has a history of multiple drug allergies	
Ferumoxytol¶	Feraheme (United States), Rienso (United Kingdom and other countries)	30 mg/mL	▪ Single dose of 1020 mg **-OR-** ▪ 2 doses of 510 mg, given 3 to 8 days apart	Not required	
Iron dextran, low molecular weight (LMW ID)Δ	INFeD (United States), Dexiron (Canada), CosmoFer (United Kingdom and other countries)	50 mg/mL	▪ Single dose of 1000 mg (diluted in 250 mL normal saline) given over 1 hour **-OR-** ▪ Multiple doses of 100 mg	Yes, 25 mg (0.5 mL) prior to the first dose	
Ferric derisomaltose (previously called iron isomaltoside)	Monoferric (United States, Canada) Monofer (United Kingdom, other countries)	100 mg/mL	▪ Weight ≥50 kg: Single dose of 1000 mg **-OR-** Up to 3 doses of 500 mg given over 7 days **-OR-** ▪ Weight <50 kg: Single dose of 20 mg/kg	Not required	
Iron sucrose (IS)	Venofer	20 mg/mL	▪ Multiple doses of 100 to 300 mg	Not required, but recommended if the patient has a history of multiple drug allergies	

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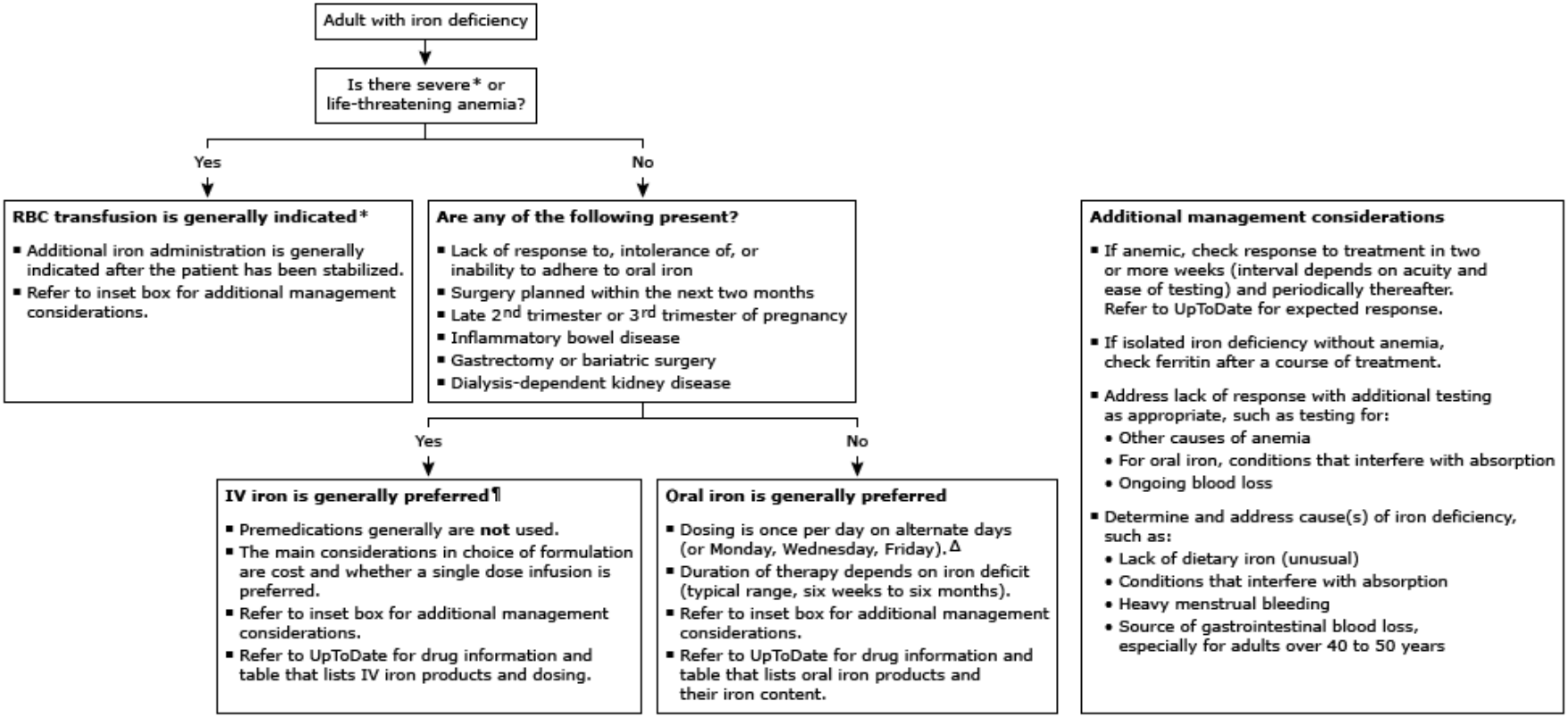
Treatment of iron deficiency (with or without anemia) in adults



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No response to iron therapy

Causes for failure to respond to oral iron therapy

Coexisting disease interfering with marrow response
Infection
Inflammatory disorder (eg, rheumatoid arthritis)
Concomitant malignancy
Coexisting folate and/or vitamin B12 deficiency
Bone marrow suppression from another cause
Patient is not iron deficient, possible correct diagnoses include
Thalassemia
Lead poisoning
Anemia of (chronic) inflammation
Copper deficiency (zinc toxicity)
Myelodysplastic syndrome/refractory sideroblastic anemia
Patient is not taking the medication
Prescription has not been filled
Prescription has been filled but patient is no longer taking the medication
Medication is being taken but is not being absorbed
Rapid intestinal transport bypasses area of maximum absorption
Enteric coated product: coating is not dissolving
Patient has acquired malabsorption for iron (eg, sprue, atrophic or autoimmune gastritis, H. pylori infection)
Medication taken in association with an agent interfering with absorption (eg, antacids, tetracycline, tea)
Congenital cause for iron malabsorption (eg, iron-resistant iron deficiency anemia, IRIDA)
Continued blood loss or need in excess of iron dose ingested
Cause of blood loss treatable (eg, bleeding peptic ulcer)
Initiate appropriate treatment
Cause of blood loss not treatable (eg, hereditary hemorrhagic telangiectasia [Osler-Weber-Rendu syndrome]) or need cannot be met by oral iron preparation (eg, renal failure or malignancy being treated with erythropoietin)
Switch patient to intravenous iron product

Assumes that original diagnosis was iron deficiency anemia with hypochromic microcytic red blood cells, low ferritin, and low transferrin saturation.

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Inherited disorders/IRIDA

IRIDA due to *TMPRSS6* mutation – Iron refractory iron deficiency anemia (IRIDA) is a **rare inherited disorder in which absorption of oral iron is markedly impaired**. IRIDA is caused by loss-of-function mutations of the TMPRSS6/matriptase 2 gene, which encodes a serine protease that cleaves membrane-bound hemojuvelin .Membrane-bound hemojuvelin promotes hepcidin synthesis and impairs iron absorption in the gut; cleavage of membrane-bound hemojuvelin reduces hepcidin synthesis, increasing iron absorption. Loss of *TMPRSS6* function thus causes iron deficiency due to inappropriately high hepcidin levels, with markedly reduced iron absorption and increased sequestration of iron in macrophages

In published case reports as well as our own experience, patients with IRIDA are not anemic at birth, and the clinical phenotype develops after the neonatal period (eg, after one month of age). Suspicion of IRIDA usually occurs during a pediatric routine evaluation. However, in some patients, the condition is recognized only in adulthood, either because the anemia is mild or because it has been misclassified. Patients present with mild hypochromic, microcytic anemia with very low serum iron levels and low transferrin saturation. Serum ferritin levels are mostly within the normal range or even slightly elevated following treatment with intravenous iron The diagnosis is pursued after elimination of causes of iron deficiency refractory to iron therapy such as celiac disease, *H. pylori* infection, autoimmune gastritis, or anemia of chronic disease/inflammation].

The diagnosis of IRIDA is confirmed by demonstrating biallelic mutation in *TMPRSS6*;

***SLC11A2* mutation** – Iron deficiency anemia has also been described in individuals with mutations in the SLC11A2 gene, which encodes the divalent metal transporter DMT1

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The outcome…

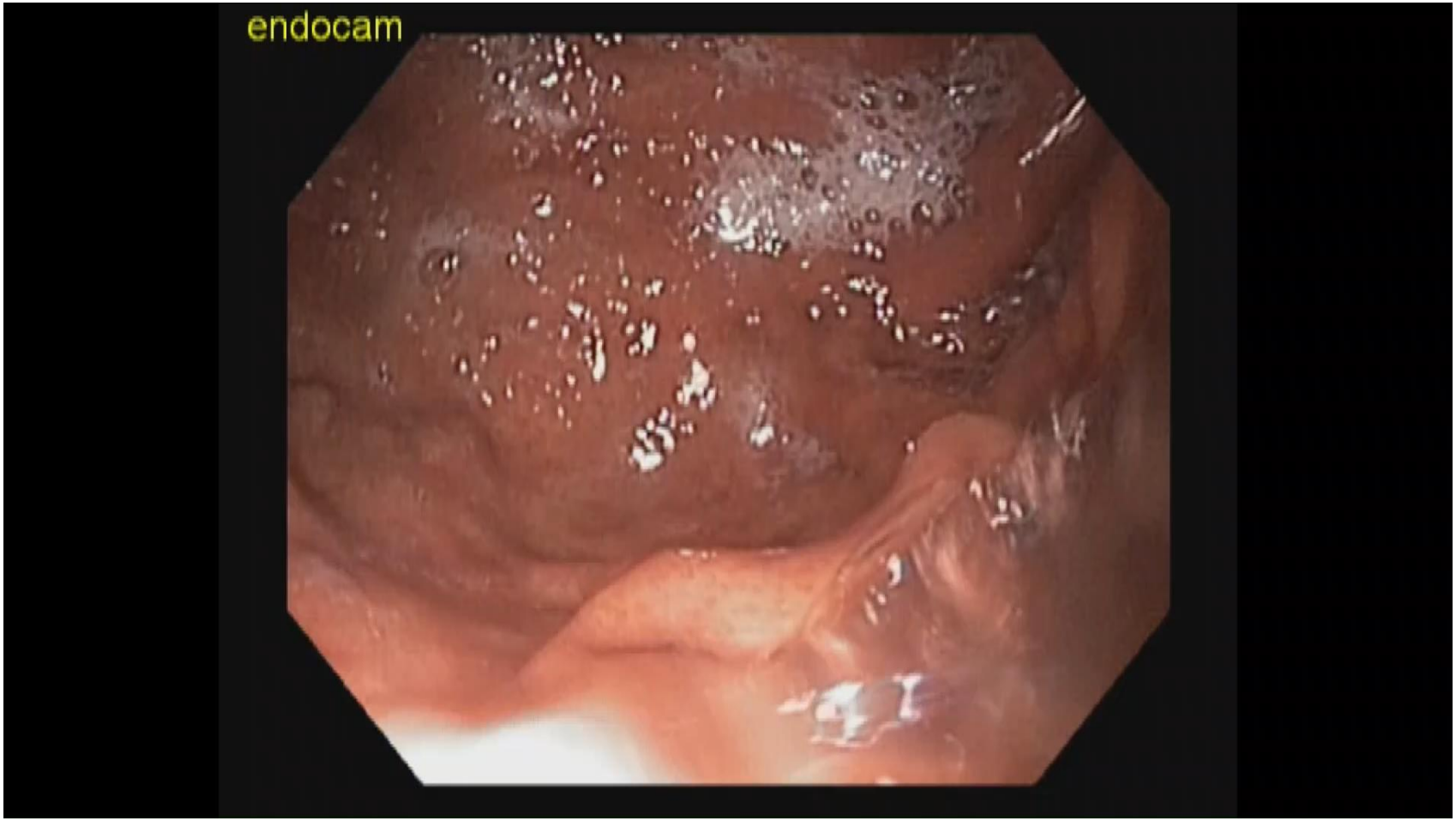
She could not tolerate po iron

She received IV iron therapy

She has still dyspeptic symptoms, epigastric discomfort.

When need upper GI endoscopy?

- Dysphagia
- Weight loss
- Bleeding
- Anemia
  - Men or postmenauposal women
- Nausea and vomiting
- Family History

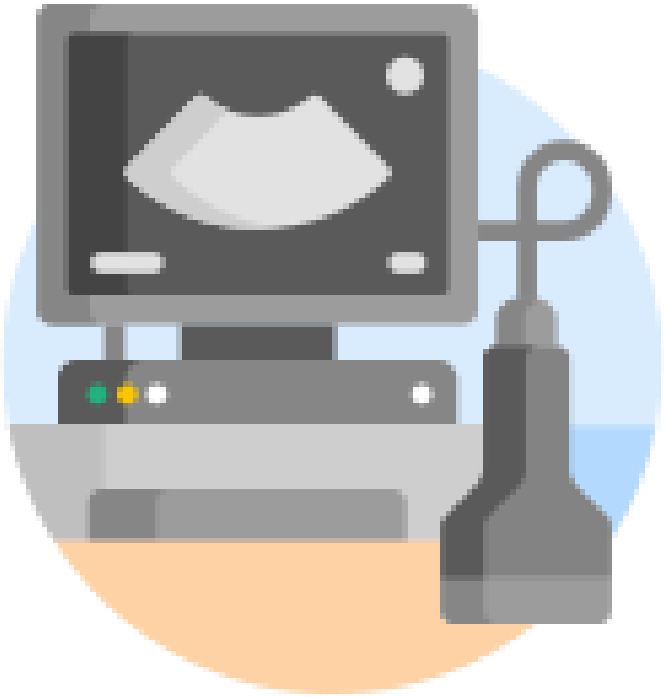


Gastric Cardia Ulcer ?

Endoscopic biopsy
2059.21-HE

What else for staging of gastric cancer?

- Complete blood cell count (CBC) and comprehensive chemistry profile
- Chest/abdomen/pelvic computed tomography (CT) with oral and intravenous contrast
- Positron emission tomography (PET) – CT evaluation if no evidence of M1 disease is found, and if clinically indicated



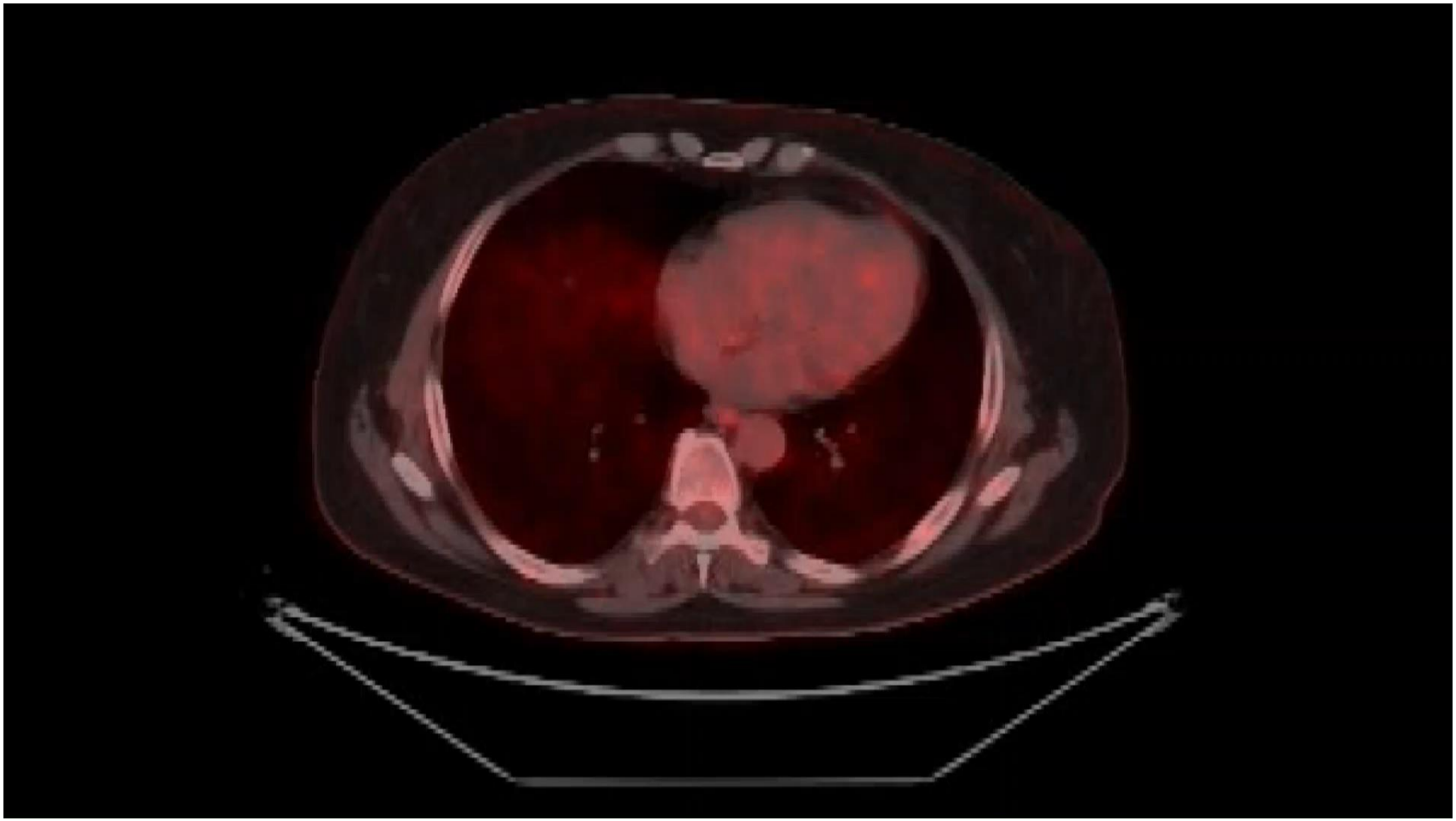
Ascites

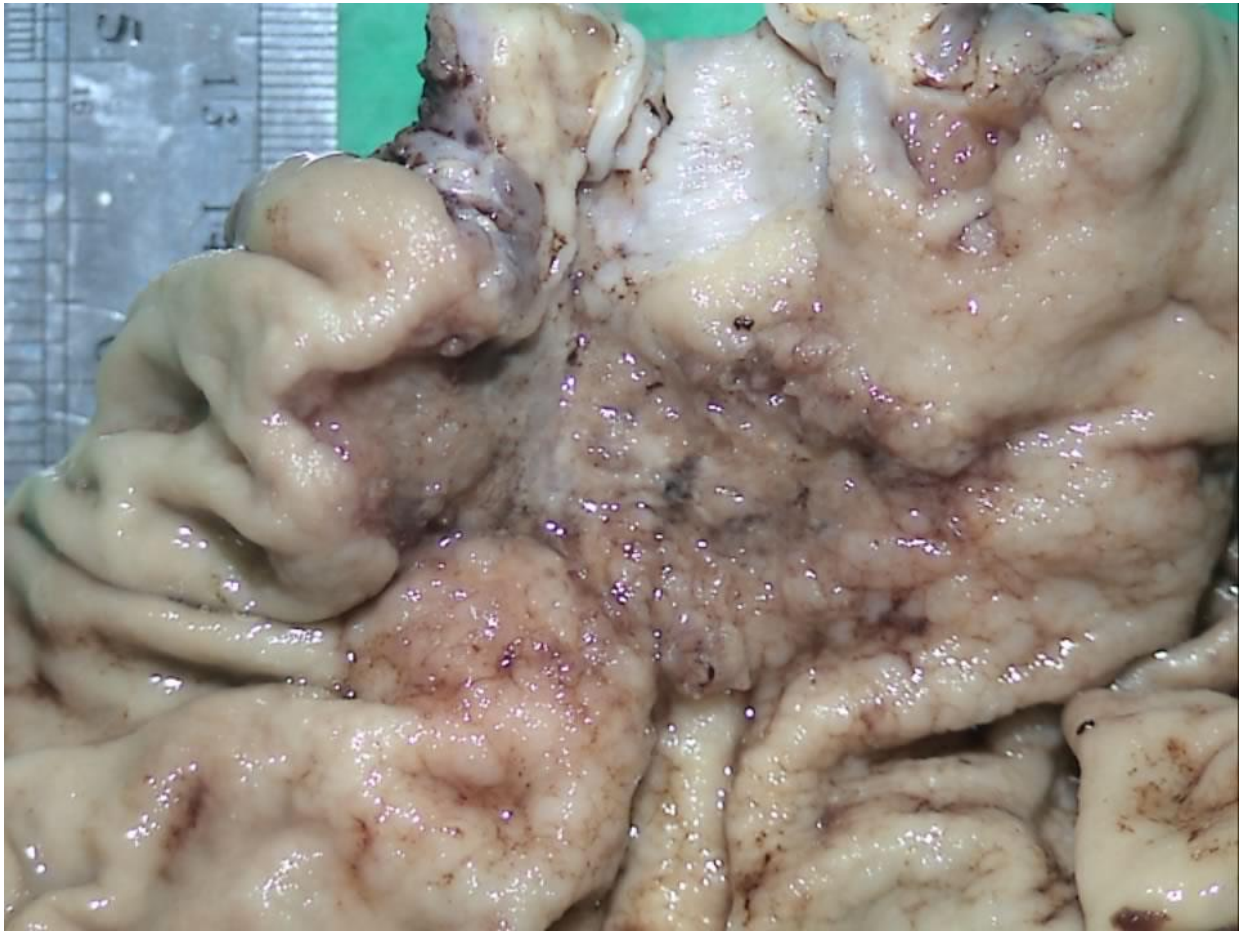
Diffuse peritoneal carinomatosis

and

Ascites

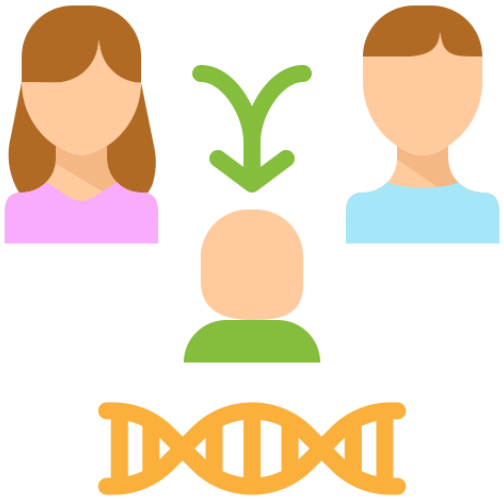
PET - CT





Is this Hereditary Cancer?

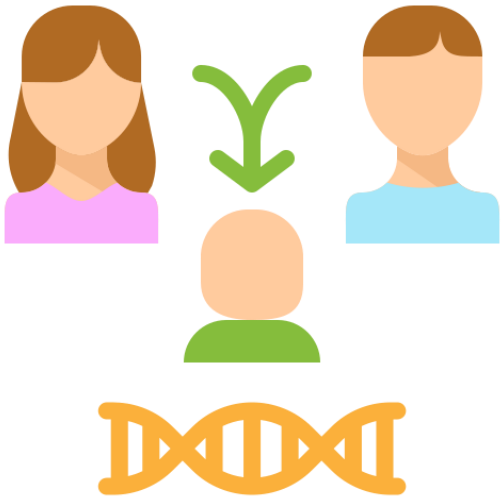
Is this Hereditary Cancer?



- A hereditary cancer syndrome is a genetic predisposition to certain types of cancer, often with onset at an early age, caused by inherited pathogenic variants in one or more genes.

- Most hereditary cancer syndromes exhibit autosomal dominant inheritance

Possible hereditary cancer syndrome



- Cancer in 2+ relatives
  - Multiple generation
  - Same side of family
- Relatives with known genetic mutations
- Young age or less than 50 years for
  - breast, ovarian, or colon cancer
- Different types of cancer in the same person
  - Include bilateral cancers
- Unusual presentation of a specific type of cancer
  - Breast cancer in a man

Table 1. Hereditary Cancer Syndromes With Increased Risks of Gastric Cancer

Syndrome	Associated gene(s)	Lifetime gastric cancer risk	Other associated cancers	Nonmalignant phenotypic features
HDGC	*CDH1*; possibly *CTNNA1*, *MAP3K6*, and others	67%–70% (males), 56%–83% (females)	Lobular breast carcinoma	Cleft lip/palate in some families
FAP	*APC*	<1%[a]	Colorectal duodenal/ampullary, thyroid, desmoid tumors, hepatoblastoma, medulloblastoma	Colorectal (and duodenal and gastric) adenomas, gastric fundic gland polyps, osteomas, CHRPE, supernumerary teeth
GAPPS	*APC* (promoter 1B region)	Undefined, but likely higher than FAP	None known	Fundic gland polyps of the proximal stomach
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	<1% to 13%[a]	Colorectal, endometrial, ovarian, urothelial, pancreatic, small-bowel, and hepatobiliary	Cutaneous sebaceous adenomas and keratoacanthomas
Li–Fraumeni syndrome	*TP53*	~5%[a]	Breast, sarcomas, lung, adrenocortical, brain (choroid plexus), leukemias, colorectal, many others	None
Peutz–Jeghers syndrome	*STK11*	~29%	Breast, pancreatic, lung, colorectal, small intestine, ovaries, testes	Hyperpigmentation of oral/genital mucosa, lips, fingers; hamartomatous polyps of GI tract, especially small bowel
Juvenile polyposis syndrome	*BMPR1A*, *SMAD4*	~21%	Colorectal and duodenal cancers	Juvenile polyps of the GI tract

CHRPE, congenital hypertrophy of the retinal pigment epithelium; GI, gastrointestinal.
[a]Risks may be higher in Asian patients.

Cell Mol Gastroenterol Hepatol 2017

Panel 1: 2020 hereditary diffuse gastric cancer (HDGC) genetic testing criteria

CDH1 testing is recommended when one of the following criteria have been met and cancer diagnoses have been confirmed. When a criterion involves two or more cancers, at least one cancer should have confirmed histology. Where possible, other relevant cancers should also be confirmed. Histologically confirmed intestinal-type gastric cancer and non-lobular breast cancer cases should not be used to fulfil testing criteria, because these cancers are not part of HDGC. Individuals who fulfil criteria for genetic testing but are found to be negative for a *CDH1* variant should subsequently be considered for *CTNNA1* analysis.

Family criteria*

1 ≥2 cases of gastric cancer in family regardless of age, with at least one diffuse gastric cancer (DGC)
2 ≥1 case of DGC at any age, and ≥1 case of lobular breast cancer at age <70 years, in different family members
3 ≥2 cases of lobular breast cancer in family members <50 years of age

Individual criteria

4 DGC at age <50 years
5 DGC at any age in individuals of Māori ethnicity
6 DGC at any age in individuals with a personal or family history (first-degree relative) of cleft lip or cleft palate
7 History of DGC and lobular breast cancer, both diagnosed at age <70 years
8 Bilateral lobular breast cancer, diagnosed at age <70 years
9 Gastric in situ signet ring cells or pagetoid spread of signet ring cells in individuals <50 years of age

*Family members must be first-degree or second-degree blood relatives of each other. Where possible, test an affected person. If there are no living affected relatives, consider tissue testing (tumour tissue or healthy tissue) from an affected deceased relative. If these options are not possible, consider indirect testing in unaffected family members.

Lancet Oncol. 2020

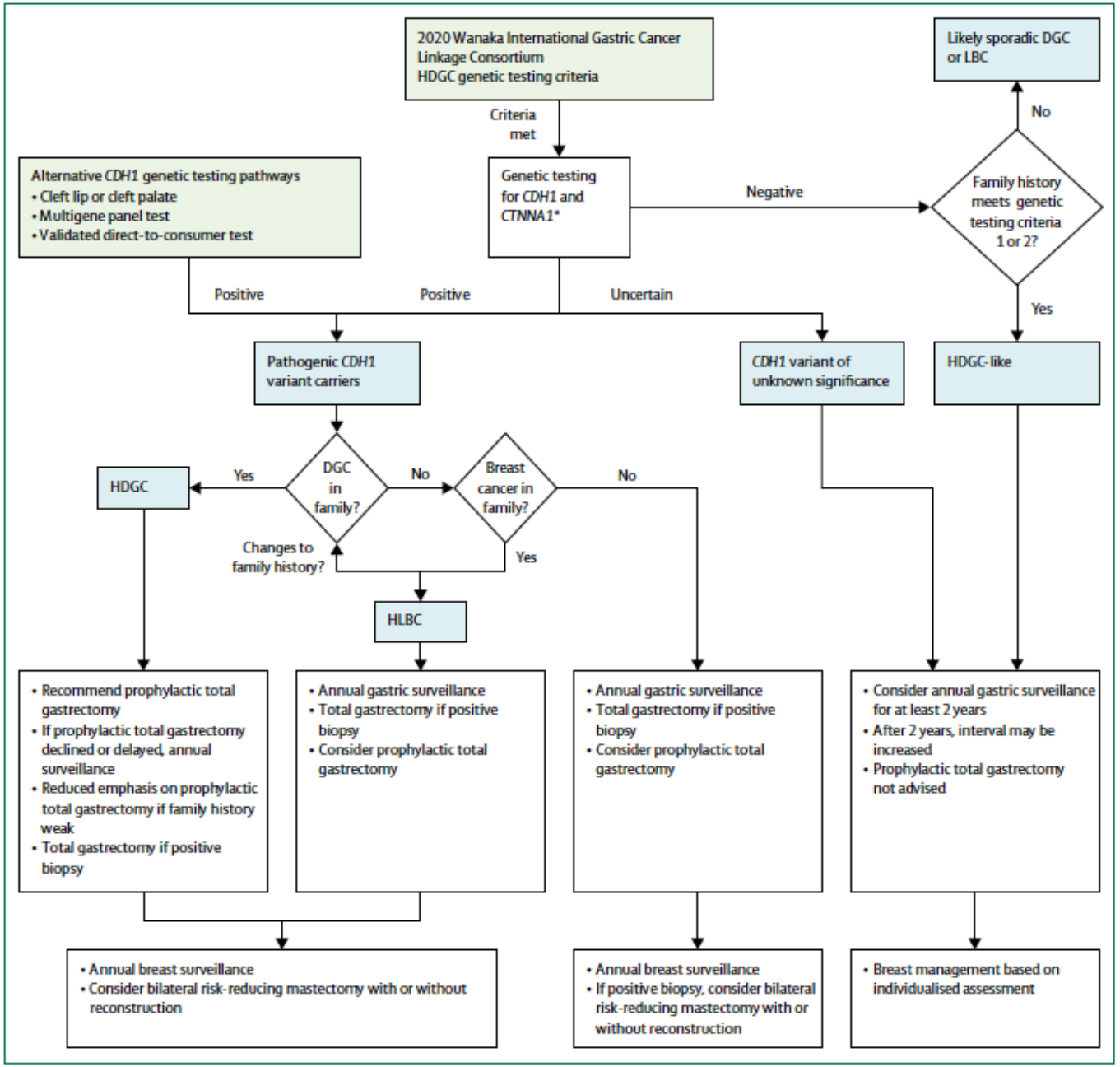
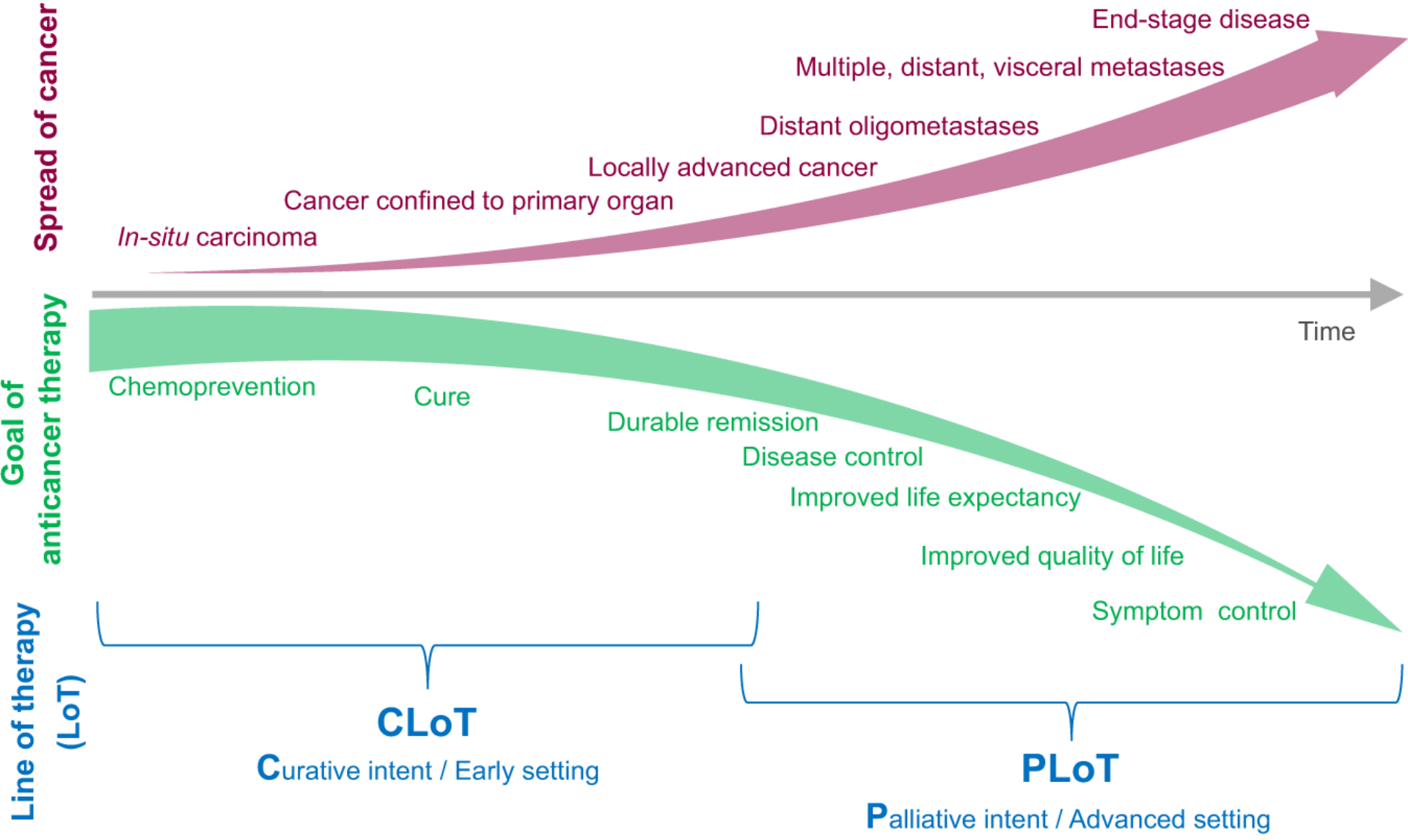


Figure 1: **Management of individuals and families who either meet the revised HDGC genetic testing criteria or have had a pathogenic *CDH1* variant identified through another route**

DGC=diffuse gastric cancer. HDGC=hereditary diffuse gastric cancer. LBC=lobular breast cancer. HLBC=hereditary lobular breast cancer. *See text for full description of *CTNNA1* pathway.

Lancet Oncol. 2020

The Goal of Cancer Treatment?



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