Primary Care Management Pathway
Iron Deficiency Anemia

Background

This primary care management pathway has been developed by a group of specialist and primary care physicians to help support the management of common non-urgent conditions with long wait-times for specialist care. These pathways are intended to help identify patients with concerning features and facilitate early referrals as needed.

Iron deficiency anemia is the most common cause of anemia worldwide. The prevalence of all causes of anemia in Canada was estimated at 3% based on data collected from 2009-2011 across 6,395 individuals across Canada.(1) This study also estimated the prevalence of iron sufficiency, which they defined as ferritin ≥ 15, finding 99% of males and 92% of females to be iron sufficient.(1) The diagnosis and treatment of iron deficiency could clearly be improved, which will improve patients quality of life. This pathway was developed to aid family physicians in the diagnosis, management, and referral of non-pregnant adults with iron deficiency anemia.

Defining Iron Deficiency Anemia

When defining iron deficiency anemia different laboratory cut-offs may be considered. The consensus for this pathway is:

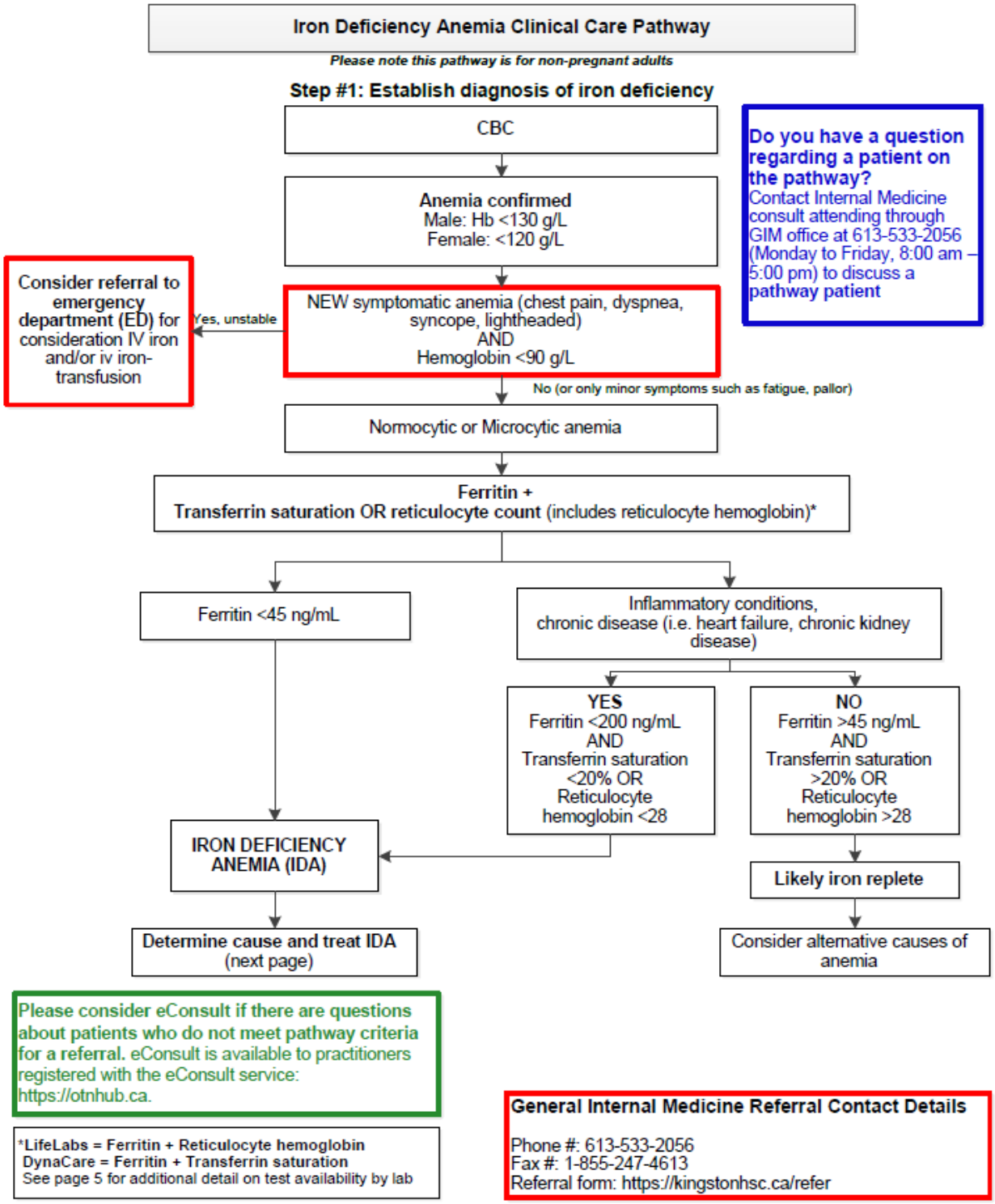
Diagnosis of iron deficiency:

- No inflammatory conditions: Ferritin <45 µg/L
  OR
- Inflammatory conditions, chronic disease (i.e. heart failure, chronic kidney disease): Ferritin <200 µg/L with either: Transferrin saturation <20% OR Reticulocyte Hemoglobin < 28

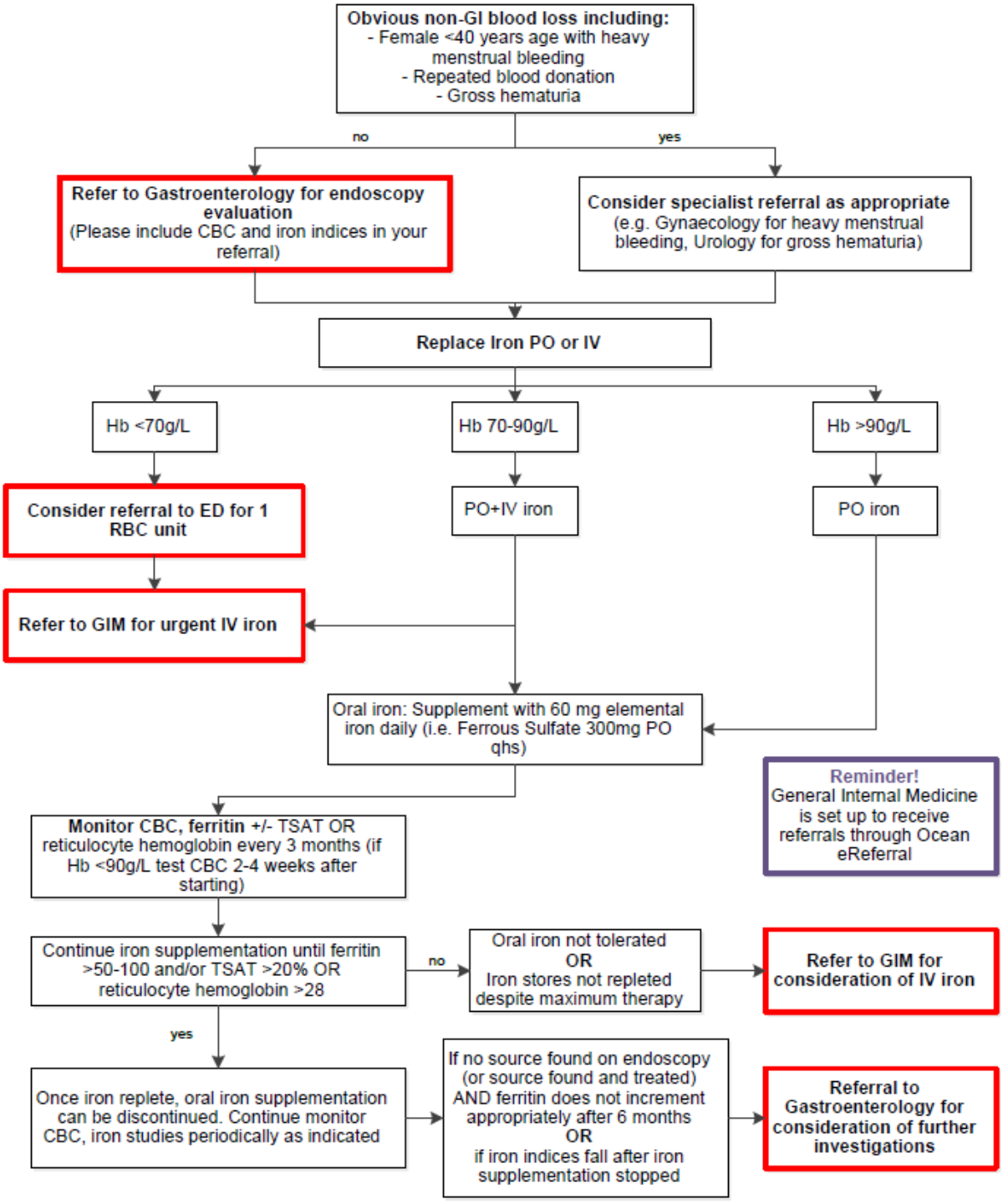
Patient information

It is possible that your patient and/or their family member may express a desire for additional information about the primary care management pathway and their role or experience throughout the process of being on a pathway. Additional information for patient education has been provided in “Appendix B – Patient Information”.

Primary Care Management Pathway – Clinical Flow Diagram
Iron Deficiency Anemia



Step #2: Determine the cause and treat iron deficiency



Appendix A – Expanded Detail

Diagnosing Iron Deficiency Anemia (IDA)

Iron deficiency anemia is typically categorized as microcytic (low MCV) and hypochromic, but can present as normocytic (normal MCV) and normochromic, particularly in its early stages. Iron deficiency results from persistently negative iron balance over time that depletes the body's iron stores. Anemia is a later manifestation of iron deficiency and not always present despite evidence of low iron stores [3].

	Iron Deficiency Anemia	Anemia of Chronic Disease
MCV	**low**/normal	**normal**/low
RDW	high	normal
Ferritin	**low**	**high/normal**
Serum Iron	low	low
Transferrin Saturation	low	low
TIBC (Transferrin)	high/normal	normal
Reticulocyte Hgb	**low**	**normal**

Table 1: Comparison of common laboratory studies in iron deficiency anemia versus anemia of chronic disease.

Serum ferritin is the most sensitive and specific test for the identification of iron deficiency (ferritin <30-45 µg/L).(2,3) However, ferritin is an acute phase reactant that may be increased in the setting of inflammation, infection or malignancy. As such, the diagnosis of iron deficiency in the setting of inflammation can be challenging. Higher cut offs for ferritin are used to define iron deficiency anemia in the context of ongoing inflammation or chronic disease; typically ferritin <200 µg/L (2). In patients with heart failure, ferritin <100 µg/L or <300 µg/L if transferrin saturation (TSAT) <20% is suggested to capture patients with both absolute and functional iron deficiency.(4) In adult patients with chronic kidney disease (CKD) and anemia, ferritin < 500 µg/L and TSAT <30% is the threshold to consider a trial of iron supplementation.(5)

While serum ferritin and TSAT are the two classic tests used to diagnose iron deficiency, we recognize the difficulties obtaining both tests in a single visit at Life Labs. The reticulocyte hemoglobin, obtained from ordering a reticulocyte count, is a useful test to use if TSAT cannot be obtained with ferritin. The reticulocyte hemoglobin content reflects the amount of iron available for hemoglobin production within the bone marrow.(6) Unlike ferritin, reticulocyte hemoglobin is not an acute phase reactant affected by inflammation. While there is a lack of consensus regarding the threshold for iron deficiency, studies suggest that a reticulocyte hemoglobin <28 pg identifies patients with iron deficiency.(7–9)

Individual laboratories have different policies for obtaining different iron studies and reticulocyte parameters. For example, LifeLabs does not process orders for ferritin and TSAT together without cost to the patient unless a valid clinical reason is stated (chronic inflammation, chronic

kidney disease, iron overload, hemochromatosis or hemosiderosis). LifeLabs will report the reticulocyte hemoglobin when you order a reticulocyte count. Through DynaCare you are not able to obtain a reticulocyte hemoglobin, as they only report reticulocyte count. However, DynaCare will allow ferritin and TSAT in all patients in a single visit without restriction.

In summary, when defining iron deficiency different laboratory cut-offs may be considered. The consensus for this pathway is:

Diagnosis of iron deficiency:

- No inflammatory conditions: Ferritin <45 µg/L
  OR
- Inflammatory conditions, chronic disease (i.e. heart failure, chronic kidney disease): Ferritin <200 µg/L with either: Transferrin saturation <20% OR Reticulocyte Hemoglobin < 28

Testing based on laboratory:

- **LifeLabs:**
  - Order Ferritin + Reticulocyte count (gives Retic hemoglobin)
  - If you want Ferritin + TSAT in a single visit, write acceptable diagnosis in additional information box (CKD, chronic inflammation, iron overload, hemochromatosis)
- **DynaCare:**
  - Order Ferritin + TSAT

Etiology of Iron Deficiency Anemia

Iron deficiency occurs with insufficient iron intake, decreased iron absorption (e.g. bowel resection, small bowel disease), increased utilization (e.g. pregnancy) and/or blood loss (most common is gastrointestinal bleeding). Please see Table 2 for causes of iron deficiency.

1. Gastrointestinal (GI) Blood Loss	
Common	Less common
Hemorrhoids, peptic ulcer disease, GI malignancy, gastritis, inflammatory bowel disease	Gastritis, esophagitis, gastrointestinal angiodysplasia
2. Non-GI Blood Loss	
Common	Less common
Heavy menstrual bleeding	Hematuria, repeated blood donation, clinical blood draws, repeated epistaxis
3. Increased iron requirements	
Pregnancy, post-bleeding recovery, use of erythropoietin	
4. Decreased Dietary Intake	
Vegetarian or vegan diet, malnutrition, alcoholism	
5. Decreased absorption	
Celiac disease, atrophic gastritis, *Helicobacter pylori*, bariatric surgery, inflammatory bowel disease	

Table 2: Common aetiologies for iron deficiency(2)

In Canada, the prevalence of iron fortified food makes insufficient intake less common, though in patients with restrictive diets this may play a role. In menstruating individuals, a detailed menstrual history is essential to identify those with heavy menstrual bleeding causing iron deficiency anemia. See the following link for resources on how to identify heavy menstrual bleeding: https://letstalkperiod.ca/nurses-resources/.

Older patients with iron deficiency anemia, with or without overt gastrointestinal bleeding, likely warrant referral to gastroenterology for consideration of endoscopy. The exceptions include menstruating females age <40, or a clear alternative cause such as other source of bleeding (e.g. hematuria, repeated blood donation). If no identifiable cause of iron deficiency can be found, consider screening for celiac disease in the appropriate patient.

Treatment of Iron Deficiency Anemia

The first step in treatment of iron deficiency anemia is identifying and treating the underlying cause. Patients with iron deficiency anemia should receive iron supplementation (oral or IV). See Table 3 for a summary of available oral iron formulations. In general, the goal is to provide ~60mg of elemental iron daily.

Formulation	Dose	Elemental Iron	Typical Dosing	Cost	Considerations
Ferrous salts					
Ferrous gluconate	300mg	35mg	300-900mg daily	$ - ODB	Least expensive Widely available
Ferrous sulfate*	300mg	60mg	300-600mg daily	$	
Ferrous fumarate	300mg	100mg	300mg daily	$ - ODB	
Other					
Polysaccharide iron (Feramax)	150mg	150mg	150mg daily	$$$	Vegan Can take w/ meal
Heme iron (Proferrin)	398mg	11mg	1 tablet TID	$$$$	Not vegan Can take w/ meal

Table 3: Oral iron formulations and their amount of elemental iron, recommended dosing and cost.(10) *ferrous sulphate 300mg PO qhs is the preferred dosing regime.

Oral iron is best absorbed on an empty stomach. Iron absorption is decreased by calcium supplements, calcium containing foods, antacids, tea/coffee, and thyroid hormone supplementation. Evidence suggests that Vitamin C supplementation does not increase absorption of oral iron.(11) If intolerable gastrointestinal side effects occur (e.g. nausea, vomiting, constipation or diarrhea), strategies to mitigate side effects include (in order of preference): reducing the dose, alternate day dosing, and changing to a different iron formulation. Ideally, we recommend Ferrous Sulfate 300mg PO qhs, as it well tolerated and contains adequate elemental iron in 1 tablet (See Appendix C for template oral iron prescription). We recognize Ferrous Sulfate is not ODB covered, so alternatively we recommend Ferrous Gluconate 600 mg PO qhs, as it may better tolerated than Ferrous Fumarate. Adequate oral iron therapy will increase hemoglobin by 10-20 g/L after 2-4 weeks.

We consider IV iron when there is severe anemia (Hgb <90), intolerance to oral iron, or inadequate response to trial of oral iron after addressing the cause of iron deficiency. Certain patient populations may benefit from IV iron including patients with IDA and: pregnancy (woman in the 2nd or 3rd trimester, especially <6 weeks from delivery), chronic kidney disease on

erythropoiesis-stimulating agents, heart failure (LVEF<45%)(12–14), or perioperative patients with IDA (time to surgery <4-6 weeks, severe anemia <100 g/dL).(15)

Formulation	Elemental iron	Recommended dose (>50kg)	LU Code	Side Effects
Iron Isomaltoside (Monoferric)	100mg/mL	1000mg once	610	Common: Fishbane reaction (flushing, dyspnea, body aches) Rare (<1%): Hypotension, Hypersensitivity reaction
Ferrous gluconate (ferrlecit) *Dialysis Patients*	12.5mg/mL	125mg per session (total cumulative dose 1000mg)	N/A	
Iron sucrose (Venofer)*	20mg/mL	300mg per session (total cumulative dose 900mg)	N/A	

Table 4: IV iron formulations and their amount of elemental iron and recommended dosing.

Monoferric (LU 610)

- Patient has documented diagnosis of IDA confirmed by laboratory testing results(e.g. hemoglobin, ferritin); AND
- Patient's IDA has experienced a failure to respond, documented intolerance, or contraindication to an adequate trial (i.e. at least 4 weeks) of at least one oral iron therapy; AND
- Patient does not have hemochromatosis or other iron storage disorders; AND
- Monoferric is administered in a setting where appropriate monitoring and management of hypersensitivity reactions can be provided to the Patient.

Authorization Period: 1 year

***Venofer EAP Criteria:** Treatment of IDA confirmed by bloodwork where the patient has demonstrated intolerance to oral iron OR has not responded to adequate therapy with oral iron. Duration of approval = 1 year.

How should I monitor patients with Iron Deficiency Anemia?

CBC, ferritin +/- transferrin saturation or reticulocyte count (includes reticulocyte hemoglobin) should be monitored approximately every 3 months if the anemia is mild. If the ferritin is <45, the ferritin alone can be used for monitoring of iron stores. If hemoglobin is <90g/L we recommend testing CBC every 2-4 weeks after starting iron supplementation to ensure appropriate increment.

If oral iron therapy is not tolerated, or patients iron stores and/or hemoglobin have not increased despite maximum oral iron therapy, then consider referral to General Internal Medicine (GIM) for possible IV iron. GIM is set up to receive referrals through Ocean eReferral.

How long should patients take oral iron supplements?

Iron supplements should be continued until ferritin >50-100 and/or reticulocyte hemoglobin >28, with resolution of anemia if present. After stopping oral iron supplementation, continue to monitor CBC and ferritin +/- reticulocyte hemoglobin periodically as clinically indicated.

If iron indices fall after iron supplementation stopped in patients with suspected source of gastrointestinal blood loss, consider re-referral to gastroenterology for further investigations.

When should I refer my patient to a specialist?

Most individuals with iron deficiency anemia can be managed by their primary care provider but there are certain instances when referral to a specialist is indicated. Which specialist to refer to is dependent on the etiology of their iron deficiency anemia.

Referral to GIM should be considered if your patient may require IV iron supplementation. This can be done early for a patient with new severe symptomatic anemia (with Hgb <90) that could be from iron deficiency, so long as they are stable enough to not warrant urgent assessment in the emergency department. Otherwise GIM will see patients who may require IV iron due to the severity of their iron deficiency anemia (Hgb <70-90) or because of intolerance of or inadequate response to oral iron therapy.

Referral to Gastroenterology should be done if your patient has red flag symptoms for underlying GI malignancy (weight loss, change in bowel habits, overt GI bleeding, compelling family history). They will also see patients where the etiology of iron deficiency anemia is not obvious, as they may consider upper endoscopy or colonoscopy to assess for occult GI bleeding.

Appendix B – Patient Information

Please note: This information is intended to be given to the patient, either as a handout or in the form of a conversation with their primary care provider.

What is "Iron Deficiency Anemia"?

Anemia means that you have low levels of hemoglobin in your blood. Hemoglobin is a component of your blood that is used to transport oxygen throughout your body and provide it to your organs including your muscles, brain, and heart. Anemia can result from many different conditions, the most common cause is low iron (called iron deficiency anemia). Iron is used to make hemoglobin, if you don't have enough iron, you cannot make red blood cells (i.e. hemoglobin). There are many causes of iron deficiency including low iron in the diet (e.g. vegan, vegetarian diets), blood loss (e.g. menstruation, blood loss in the gut), inability to absorb iron in the gut, or increased iron utilization (e.g. during pregnancy). People with anemia may experience several symptoms related to low blood levels and low iron, such as fatigue, chest pain, shortness of breath, weakness, light-headedness, or restless legs at night time.

How will my doctor follow my condition?

Once a diagnosis of iron deficiency anemia is made, your doctor will need to determine the cause of iron deficiency to determine the next steps. Depending on the most likely cause of iron deficiency, or if they are unsure of the cause, you may be referred to a specialist for further testing. Otherwise, you will be started on iron supplementation and your doctor will check your blood work every few months to ensure improvement. When your iron deficiency and anemia resolved you may be able to come off your iron supplements and your family doctor will continue to check your blood work periodically to ensure your iron deficiency anemia does not recur.

You are enrolled on a "Iron Deficiency Anemia" clinical pathway. What does this mean?

The "Iron Deficiency Anemia" clinical pathway was developed by family doctors, internists, hematologists and other specialists at Kingston Health Sciences Centre to help with the screening and treatment of people with iron deficiency anemia. Clinical pathways are an evidence-based tool for common conditions seen frequently by family doctors. The pathways ensure that patients receive standardized care for their conditions. Clinical pathways help identify patients with high risk features and facilitate early referral to specialists as needed. They also identify patients with low risk disease who can be monitored by their family doctors.

Appendix C – Oral Iron Prescription Form

ORAL IRON PRESCRIPTION FORM

Date: _____

PATIENT IDENTIFICATION

Prescription

Ferrous Sulfate 300 mg PO QHS

Dispense: 90 days

Refill: 3

Physician (print): _____ Signature: _____MD

Contact #: _____

CPSO #: _____

ORAL IRON PRESCRIPTION FORM

Date: _____

PATIENT IDENTIFICATION

Prescription
Ferrous Gluconate 600 mg PO QHS
Dispense: 90 days
Refill: 3

Physician (print): _____ Signature: _____MD

Contact #: _____

CPSO #: _____

Appendix D – Endnotes

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