Primary Care Management Pathway
Erythrocytosis

Background

Primary care management pathways (PCMP) are being co-developed by primary care physicians (PCP) and specialists to support the management of common, non-urgent conditions for which long wait times to specialty care currently exist. This erythrocytosis pathway will help differentiate patients with high-risk features who require timely specialist assessment from those who can be safely managed by their PCP.

Erythrocytosis (also called polycythemia) refers to a hemoglobin concentration and/or a hematocrit level above the sex-specific normal range (1, 2). Erythrocytosis can be classified as relative polycythemia, caused by a reduction in plasma volume, or as absolute polycythemia, caused by an increase in red cell mass. Absolute polycythemia can be further subcategorized as primary erythrocytosis, an increased autonomous production of erythrocytes usually due to a myeloproliferative neoplasm (polycythemia vera [PV]), or secondary erythrocytosis, an increase in red blood cell (RBC) mass from a physiological response to increased erythropoietin (EPO) levels.

Erythrocytosis can affect up to 4% of ambulatory men and 0.4% of ambulatory women in Canada based on hemoglobin levels of greater than 165 g/L or 160 g/L, respectively (1). However, the overall incidence rate of PV is approximately 1.57 per 100000 person-years (3). Determining the specific cause for erythrocytosis, and especially differentiating PV from other causes of erythrocytosis, is critical to ensure appropriate patient management.

Defining erythrocytosis (3)

- Elevated hemoglobin concentration (> 165 g/L in men; > 160 g/L in women) or elevated hematocrit (> 0.49 in men; > 0.48 in women)

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”

Version date: September 2026

Primary Care Management Pathway – Clinical Flow Diagram

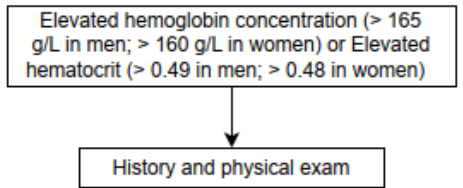
ngston Health
iences Centre
ntre des sciences de
anté de Kingston

Hôpital
Hotel Dieu
Hospital

KGH Hôpital Général de
Kingston General
Hospital

Box 1

Red flags:
Extremely raised hematocrit
(Male > 0.6, Female > 0.56) in
the absence of congenital



1. Urgent hematology
2. Start low-dose aspi
RED FLAG from abno
OR platelet count > 1

Box 2: Evaluation of secondary erythrocytosis

Etiology	Investigations or interventions to consider
Hypoxia: Interatrial shunt (Patent foramen ovale / atrial septal defect with R→L shunting) Pulmonary hypertension Chronic lung disease Smoking-related hypoxia Carbon monoxide poisoning Sleep apnea	 Pulse oximetry Chest X-ray Exercise oximetry* + CT chest (if dyspnea and/or ≤94% O2 saturation on room air at rest) Carboxyhemoglobin level Smoking cessation Pulmonary function tests (including DLCO) Echocardiogram (with bubble study to rule out shunting) Overnight oximetry +/- polysomnography
Inappropriate EPO secretion: Hepatic/renal tumours Uterine Fibroids	 Liver studies Renal studies Abdominal and/or pelvic imaging
Medications SGLT2 inhibitors Testosterone	 Consider dose reduction (e.g. testosterone) or temporary interruption (e.g. SGLT2 inhibitor) of offending medication to prove causal relationship**

*A suggested method for exercise oximetry is to perform continuous monitoring of pulse oximetry during a 6 minute walk test.

**Risk of complications from secondary erythrocytosis (i.e. thrombosis) are lower in secondary erythrocytosis compared to primary erythrocytosis (12). Therefore, temporarily interrupting or reducing the dose of the offending medication is reasonable in the context of investigating erythrocytosis, if the prescribing physician judges that there is a significant benefit to long-term continuation of the medication.

Appendix A – Expanded Detail

How is erythrocytosis defined?

Erythrocytosis is an elevated hemoglobin concentration (> 165 g/L in men; > 160 g/L in women) and/or hematocrit level (> 0.49 in men; > 0.48 in women) in the peripheral blood (3).

What are the etiologies of erythrocytosis?

Erythrocytosis can be relative, due to a reduction in plasma volume (e.g. dehydration, diuretics, smoking) or absolute, due to an increase in RBC mass. Absolute erythrocytosis can be primary, due to an increased autonomous production of erythrocytes, or secondary, due to external factors outside the bone marrow stimulating erythropoiesis – mainly increased erythropoietin (EPO) production. When the etiology of erythrocytosis is unclear despite extensive testing, it is labeled as "idiopathic erythrocytosis," a diagnosis of exclusion (4).

Most common causes of erythrocytosis are shown below: (1, 2, 4-8)

Table 1. Differential diagnosis of erythrocytosis

Relative erythrocytosis (decreased plasma volume)	
• Dehydration • Vomiting • Diarrhea • **Diuretic use** • **SGLT2 inhibitor use** • *Gaisböck's syndrome* ○ Erythrocytosis in anxious/tense patients who are hypertensive, have normal spleen size, and reduced plasma volume. It is debated whether this clinical entity actually exists.	
Absolute erythrocytosis (increased red blood cell mass)	
1-Primary erythrocytosis (uncommon)	
Congenital	• *EPOR* mutation • *SH2B3 (LNK)* mutation • Oxygen-sensing pathway gene mutations such as in *VHL, EGLN1 (PHD2), EGLN2 (PHD1) EPAS1 (HIF2A)* • High oxygen-affinity hemoglobins • Gain-of-function mutation in the *EPO* gene • Methemoglobinemia • Bisphosphoglycerate mutase deficiency • *SLC30A10* mutations with hypermagnesemia

	• Hereditary increase in adenosine triphosphate • *PIEZO1* gene mutation
Acquired	• **Polycythemia vera**
2-Secondary (common)	
Central hypoxia	• **Chronic lung disease** • Right-to-left cardiopulmonary shunts • Living at high altitude • **Obstructive sleep apnea** • **Smoking** • Chronic carbon monoxide exposure • Massive obesity (Pickwickian syndrome)
Renal hypoxia	• Renal artery stenosis
EPO producing tumours	• Cerebellar hemangioblastoma • Renal cell carcinoma • Hepatocellular carcinoma • Uterine leiomyoma • Pheochromocytoma • Meningioma • Parathyroid carcinoma/adenoma
Drugs	• Erythropoiesis-stimulating agents • Androgen preparations • **Testosterone**
Miscellaneous	• Alcohol excess • Post renal transplant • Adrenal disorders: Cushing's syndrome • TEMPI (Telangiectasis, Elevated erythropoietin and erythrocytosis, Monoclonal gammopathy, Perinephric fluid, Intrapulmonary shunting) syndrome • POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, Skin changes) syndrome • Cobalt toxicity
3-Idiopathic erythrocytosis	
No cause identified. This is a diagnosis of exclusion.	

How to approach the workup of erythrocytosis?

A significant erythrocytosis, defined as an elevated hemoglobin concentration (> 165 g/L in men; > 160 g/L in women) and/or hematocrit level (> 0.49 in men; > 0.48 in women), requires further investigation.

The first step in evaluation is a complete history, physical exam, and review of the CBC with differential to investigate for potential etiology (see **Table 1**) and to evaluate for **RED FLAGS** (see **RED FLAGS** listed below) (9). If present, **RED FLAGS** would necessitate urgent referral to Hematology. It is also reasonable to start low-dose aspirin (unless the **RED FLAG** is from abnormal bleeding, if the platelet count is over 1000, or if the patient is already taking an antiplatelet or anticoagulant medication). The following investigations should also be sent: JAK2 testing **(see section entitled "What is JAK2/EPO testing?" on how to order)**, LDH, ferritin, renal and liver panel. Serum EPO level testing may be helpful but is optional; the patient will need to pay out-of-pocket if the test is performed at external laboratories **(see section entitled "What is JAK2/EPO testing?" on why the utility of this test is limited, and how to order it if desired)**.

Clinical evaluation is a critical first step in the investigation of erythrocytosis because the appropriate subsequent investigations depend on what the suspected underlying etiology(ies) is(are) (10). The history and physical examination should aim to rule out relative erythrocytosis and then differentiate between primary and secondary erythrocytosis. For secondary erythrocytosis, this includes a review of cardiac, pulmonary, and gastrointestinal signs and symptoms. Patients should be asked about lifestyle habits (especially smoking) medications (especially anabolic steroids, testosterone, diuretics, and SGLT2 inhibitors), exposure to carbon monoxide, and symptoms of sleep apnea. A cardiopulmonary exam should be performed as well as an abdominal exam for organomegaly or EPO-producing intra-abdominal tumours (e.g. hepatocellular or renal cell carcinoma) (1, 2). An oxygen saturation less than 92% on room air by pulse oximetry can suggest hypoxic cardiopulmonary disease (8).

For primary erythrocytosis, it is important to pay attention to thrombosis and bleeding history, especially a history of thrombosis at unusual sites (eg. mesenteric, hepatic, portal, cerebral veins, arterial thromboses). On history, symptoms to look for that raise suspicion for polcythemia vera include:

- Hyperviscosity symptoms, which can manifest as chest or abdominal pain, fatigue, headache, blurred vision, and slow mentation.
- Constitutional symptoms including fever, excessive sweating, and weight loss
- Pruritus (especially after bathing or taking a hot shower [aquagenic pruritus]) and erythromelalgia (intense, burning pain and/or redness of the extremities)
- Gout
- Early satiety (due to splenomegaly)

On physical exam, plethoric facies and areas of painful erythema may be seen, and the abdominal exam is key to search for hepatosplenomegaly which also raises the suspicion for polycythemia vera (11).

If no RED FLAGS are present, then investigate as follows:

- Repeat CBC in 2 weeks
    - If erythrocytosis resolves, repeat CBC in 3 months. If both results show ongoing resolution
        - Discontinue monitoring
    - If erythrocytosis persists after 2 weeks, or if erythrocytosis initially resolves but then recurs on repeat CBC 3 months later:
        - Perform JAK2 testing **(see section entitled "What is JAK2/EPO testing?" on how to order)**, LDH, ferritin, renal and liver panel. Serum EPO level testing may be helpful but is optional; the patient will need to pay out-of-pocket if the test is performed at private laboratories **(see section entitled "What is JAK2/EPO testing?" on why the utility of this test is limited, and how to order it if desired)**.
        - If history/physical suggest a secondary cause (or causes) for erythrocytosis (see **Table 1**), begin completing additional investigations as needed (see **Table 2** below for suggestions)

For patients undergoing JAK2 testing:

- If JAK2 mutation is found (positive), this is suspicious for PV regardless of EPO level (if EPO level is performed). **Please send a referral to hematology**. Start low-dose aspirin while waiting for patient to be assessed by hematology (unless abnormal bleeding or the patient is already taking an antiplatelet or anticoagulant medication).
- If JAK2 mutation is not found (negative), but serum EPO level is low (if EPO level is performed), this is also suspicious for PV, therefore **please send a referral to hematology**. Start low-dose aspirin while waiting for patient to be assessed by hematology (unless the patient is already taking an antiplatelet or anticoagulant medication).
- If JAK2 mutation is not found (negative) and serum EPO level is normal/high (if EPO level is performed) or unknown, secondary erythrocytosis is more likely. Investigate and treat secondary causes if not previously done (see **Table 2** for investigations).
    - If additional investigations do not reveal an obvious secondary cause, refer non-urgently to hematology
    - If additional investigations reveal a secondary cause (or causes), which cannot be modified or treated, monitor the patient clinically and with CBC's every 3 months. The patient likely has secondary erythrocytosis, but may still develop symptoms or complications (e.g. thrombosis). Refer to hematology if the patient develops **RED FLAGS** or if hematocrit is persistently above 0.55 (for consideration of phlebotomy).
    - If additional investigations reveal a secondary cause (or causes) which can be successfully treated, repeat the CBC in 4 weeks and 3 months to ensure erythrocytosis improves / resolves
        - If erythrocytosis improves/resolves, monitor CBC every 3 months until resolution
        - If erythrocytosis persists, refer non-urgently to hematology

Table 2: Evaluation of secondary erythrocytosis

Etiology	Investigations or interventions to consider
Hypoxia: Interatrial shunt (Patent foramen ovale / atrial septal defect with R→L shunting) Pulmonary hypertension Chronic lung disease Smoking-related hypoxia Carbon monoxide poisoning Sleep apnea	 Pulse oximetry Chest X-ray Exercise oximetry* + CT chest (if dyspnea and/or ≤94% O2 saturation on room air at rest) Carboxyhemoglobin level Smoking cessation Pulmonary function tests (including DLCO) Echocardiogram (with bubble study to rule out shunting) Overnight oximetry +/- polysomnography
Inappropriate EPO secretion: Hepatic/renal tumours Uterine Fibroids	 Liver studies Renal studies Abdominal and/or pelvic imaging
Medications SGLT2 inhibitors Testosterone	 Consider dose reduction (e.g. testosterone) or temporary interruption (e.g. SGLT2 inhibitor) of offending medication to prove causal relationship**

*A suggested method for exercise oximetry is to perform continuous monitoring of pulse oximetry during a 6 minute walk test.

**Risk of complications from secondary erythrocytosis (i.e. thrombosis) are lower in secondary erythrocytosis compared to primary erythrocytosis (12). Therefore, temporarily interrupting or reducing the dose of the offending medication is reasonable in the context of investigating erythrocytosis, if the prescribing physician judges that there is a significant benefit to long-term continuation of the medication.

What is JAK2 testing/EPO testing?

EPO testing is a peripheral blood test that measures the amount of erythropoietin in the blood, a hormone produced in the kidneys that stimulates erythrocyte proliferation (4). An increase in EPO can be due to an appropriate physiologic response to hypoxia, an inappropriate autonomous production of EPO (eg, EPO-secreting tumor), or exogenous administration (eg, erythropoietin stimulating agents). Causes of elevated EPO are described above (see **Table 1**). In contrast, a subnormal level of serum EPO in a patient with erythrocytosis suggests primary erythrocytosis from polycythemia vera (4). Other rarer causes of erythrocytosis with subnormal EPO levels include "blood doping" (transfusing one's own red blood cells to enhance athletic performance) (2), an EPO receptor mutation causing congenital erythrocytosis (13), and occasionally in post-renal transplant erythrocytosis (some evidence to support that post-transplant erythrocytosis is caused by inappropriate EPO production of native kidney and/or allograft, however other evidence showing some of these patients having low/undetectable EPO levels) (14).

JAK2 is a tyrosine kinase that plays a role in stimulating hematopoietic cell proliferation, including erythrocytes. A specific mutation in the JAK2 gene, known as V617F, has been found in the cells of patients with myeloproliferative neoplasms such as PV, and leads to persistent activation of JAK2 which can result in erythrocytosis (15). In cases of PV where the JAK2V617F mutation is negative, the majority of cases will have a mutation in JAK2 exon 12 (16). The JAK2 test is a blood test in molecular genetics that utilizes a laboratory technique called polymerase chain reaction (PCR), where DNA from patient cells are rapidly amplified, allowing for the detection of mutations (17) such as the JAK2 V617F mutation or mutations in JAK2 exon 12. At Kingston Health Sciences Center, JAK2 mutation testing is not performed in isolation but rather as part of a more comprehensive "MPN panel," which also tests for mutations in calreticulin (CALR) and myeloproliferative leukemia virus oncogene (MPL), genes that can be mutated in other myeloproliferative neoplasms such as essential thrombocytosis and primary myelofibrosis (18).

The main purpose of EPO level and JAK2 testing in patients with erythrocytosis is to help determine if erythrocytosis is due to a primary or secondary cause. This can help decide whether to refer to hematology directly or investigate for secondary causes of erythrocytosis first.

JAK2 testing is free of charge to the patient as it will be covered under the Community Access Pilot for Laboratory Services Program by the Ministry of Health of Ontario. Please see requisitions in **Appendix C** that need to be filled out to submit this test. Serum EPO level testing may be helpful but is optional; the patient will need to pay out-of-pocket if the test is performed at external laboratories. EPO level testing is optional because the utility of this test is limited. If the level is low, it may identify JAK2 negative PV (only approximately 2% of cases), however, if levels are normal to high, it does not rule out JAK2+ PV. Therefore, JAK2 testing remains the more informative test when investigating erythrocytosis.

To order JAK2 testing, you will need an Ontario external laboratory requisition, and requisition from Kingston Health Sciences Center for molecular testing. Please see **Appendix C**. This testing can be performed at any community laboratory. To order a serum EPO level if desired, take an Ontario external laboratory requisition, and in the section marked "Other Tests – one test per line," write "serum EPO level."

What is polycythemia vera?

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by erythrocytosis and is often accompanied by leukocytosis and thrombocytosis. The JAK2V617F mutation, found in approximately 95% of PV patients, results in constitutive JAK-STAT signaling which is responsible for the pathogenesis of PV (15).

PV has an estimated incidence of approximately 2.8 per 100,000 among men and 1.3 per 100,000 in women with a prevalence of 22 cases per 100,000 (6). Patients are usually diagnosed in the 6th decade of life, but up to one third of patients can present before age 50 (19).

Most patients are diagnosed incidentally by bloodwork and are asymptomatic of their erythrocytosis. In symptomatic patients, there are multiple ways with which patients may present. Hyperviscosity from erythrocytosis can lead to non-specific symptoms such as headache, weakness, dizziness, and excessive sweating. Patients may complain of pruritus, especially after

taking hot baths or showers (aquagenic pruritus), and/or erythromelalgia, a combination of erythema and burning sensation in the hands/feet. Patients with splenomegaly may have abdominal symptoms such as early satiety. Some patients are also discovered to have PV in the setting of a thrombotic event (11).

Polycythemia vera should be suspected in patients with persistent, unexplained erythrocytosis, defined as hemoglobin > 165 g/L in men and > 160 g/L in women or hematocrit > 0.49 in men and > 0.48 in women. The criteria for diagnosing PV are presented below (20).

Table 3. Diagnostic criteria for polycythemia vera per WHO (3) and ICC 2022 (20)

ICC	WHO
Major criteria 1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass* 2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation† 3. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia Minor criterion • Subnormal serum erythropoietin level	Major criteria 1. Elevated haemoglobin concentration (> 165 g/L in men; > 160 g/L in women) or Elevated haematocrit (>0.49[a] in men; >0.48 in women) 2. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)[b] 3. Presence of JAK2 V617F or JAK2 exon 12 mutation Minor criterion • Subnormal serum erythropoietin level.
The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion‡	The diagnosis of polycythaemia vera requires either all 3 major criteria or the first 2 major criteria plus the minor criterion.
* Diagnostic thresholds: hemoglobin: > 165 g/L in men and > 160 g/L in women; hematocrit: > 0.49 in men and > 0.48 in women; red blood cell mass: > 25% above mean normal predicted value. † It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level < 1%); in negative cases, consider searching for noncanonical or atypical *JAK2* mutations in exons 12 to 15. ‡ A bone marrow biopsy may not be required in patients with sustained absolute erythrocytosis (hemoglobin concentrations of >185 g/L in men or >165 g/L in women and hematocrit values of >0.555 in men or >0.495 in women) and the presence of a *JAK2* V617F or *JAK2* exon 12 mutation.	a Haematocrit for diagnosis in the absence of a JAK2 mutation. A higher haematocrit target could be considered (e.g., 0.52) in men before further investigation may be required. b Major criterion 2 (bone marrow biopsy) may not be required in patients with sustained absolute erythrocytosis (haemoglobin concentrations of > 185 g/L in men or > 165 g/L in women or haematocrit values of > 0.555 in men or > 0.495 in women), if major criterion 3 and the minor criterion are present. The determination of the red cell mass with 51Cr-labeled red cells allows the differentiation between true polyglobulia and pseudopolyglobulia. This is not a method for routine clinical use.

As such, JAK2 mutation testing and erythropoietin levels should be performed when PV is suspected. PV is highly likely if JAK2 mutation is present and EPO levels are subnormal. In other cases, bone marrow biopsy may be necessary to confirm the diagnosis of PV and/or distinguish from other MPNs.

PV leads to a reduced life expectancy with an estimated 10-year survival being 28% lower than the general population (21). However, unlike other hematologic malignancies, the main cause of morbidity and mortality in patients with PV is thrombosis, both venous and arterial. The incidence of thrombosis is approximately 18/1000 person-years in patients with PV and is responsible for approximately 45% of deaths related to PV (22). Rarer but significant complications of PV include transformation to myelofibrosis (4.9-6% of patients in 10 years and 6-14% of patients in 15 years) (3), a condition characterized by excessive fibroblastic proliferation of the bone marrow, and another complication is transformation to acute leukemia (2.3-14.4% of patients in 10 years and 5.5-18.7% of patients in 15 years) (3). Because of these potentially serious consequences, suspected and confirmed cases of PV should be referred to hematology for proper evaluation and treatment. If PV is confirmed, treatment is non-curative but rather aims to reduce complications and symptoms, and usually involves phlebotomies to target a hematocrit less than 0.45, low-dose aspirin, and cytoreductive therapies such as hydroxyurea in patients with higher risk of thrombosis (23). PV patients on treatment will be regularly followed by hematology to monitor disease control and side effects of therapy. From a primary care perspective, it is especially important to optimize management of atherosclerotic risk factors such as hypertension, dyslipidemia, diabetes, obesity, and smoking cessation because of the increased risk of thrombosis (6).

My patient has persistent erythrocytosis, now what?

Explain the diagnosis to your patient.

1. For suspected secondary erythrocytosis:

“This is a condition where your body is producing red blood cells at a higher-than-normal rate that appears as a reaction to an underlying condition. In your bloodwork, this is measured as an increased hemoglobin and/or hematocrit level. The treatment for this condition is to find the underlying cause and treat it. Once the underlying cause is identified and treated, the hemoglobin level/hematocrit level should normalize and will not need further monitoring. However, if the underlying cause cannot be corrected, hemoglobin/hematocrit levels will likely require lifelong monitoring.”

2. For suspicion of PV:

“Polycythemia vera, or "PV," is a condition that affects bone marrow. The bone marrow is responsible for making blood cells. People with PV make too many red blood cells - the cells that carry oxygen to tissues in the body. They might also have higher-than-normal levels of white blood cells – the cells that fight off infections, and platelets – these are responsible for blood clotting to stop bleeding after an injury. People with PV can be completely asymptomatic, or present with a variety of symptoms, including headaches, weakness or dizziness, vision problems, excessive sweating, decreased appetite and feeling full after only a small amount of food, itchiness especially after a hot bath or shower and redness and burning in the hands and feet. PV can be diagnosed by

blood tests but sometimes requires a bone marrow biopsy. You will be referred to a hematologist to help guide further evaluation and management. PV is associated with potential complications, the most common one being blood clots, but in rarer cases, progression to myelofibrosis – an excess of scar tissue in the bone marrow, and progression to leukemia – a type of aggressive blood cancer where too many white blood cells are produced. Treatment for polycythemia vera is not curative, but rather aims to reduce complications, especially blood clots. First, adopting healthy lifestyle habits such as a balanced diet, regular exercise, and smoking cessation, is encouraged. Screening for other health issues that increase the risk of blood clots, such as hypertension or diabetes, and optimizing management of these risk factors if present, will also be considered. Your hematologist may also initiate a procedure called phlebotomy, which involves removing blood from your body, similar to when giving a blood donation. However, please do not volunteer to donate blood to Canadian Blood Services while you are under investigation for PV, as people with this blood condition are ineligible to donate blood. You will also be prescribed low-dose aspirin which helps prevent blood clots (unless you are already taking a blood thinner). You may also be prescribed medication that reduces the amount of red blood cells made by the bone marrow, the most common being hydroxyurea. Monitoring this disease will become part of your routine follow up like other chronic conditions such as high blood pressure or diabetes. During treatment, you will see the hematologist regularly and get blood tests. This is to ensure that the treatment is working, to monitor for side effects, and to monitor for complications of the condition."

3. For unexplained erythrocytosis

"This is a condition where your body is producing red blood cells at a higher-than-normal rate, but no underlying cause has been identified. When no underlying cause is found, this is called "idiopathic erythrocytosis". You will be referred to a hematologist for a recommendation on further evaluation and management."

When should I refer my patient with erythrocytosis to a Hematologist?

1. If any of the following **RED FLAG** symptoms are present:

- Extremely raised hematocrit (Male > 0.6, Female > 0.56) in the absence of congenital cyanotic heart disease
- Persistently raised haematocrit (Male > 0.49, Female > 0.48) in association with:
    - Recent arterial or venous thrombosis (including DVT / PE, CVA / TIA, MI /unstable angina, PVD)
    - Unexplained neurological symptoms
    - Visual loss
    - Abnormal bleeding
    - Pruritus / erythromelalgia
    - Splenomegaly
    - Neutrophil and/or platelet count above upper limit of normal
    - Family history of erythrocytosis

2. If JAK2 testing is positive.

3. In the event that no secondary cause is identified in a patient with JAK2-negative erythrocytosis.

When should I stop monitoring erythrocytosis?

For relative polycythemia or secondary erythrocytosis, it is reasonable to discontinue monitoring of erythrocytosis after treatment of the underlying disorder leads to resolution of the erythrocytosis. For other clinical scenarios, lifelong monitoring will likely be required.

Appendix B – Patient Information

WHAT IS ERYTHROCYTOSIS?

Erythrocytosis is a condition where there is a higher-than-normal concentration of red blood cells (erythrocytes) in the blood.

Erythrocytosis may be

- Primary: red blood cell production increases in your bone marrow, the primary site in the body where red blood cells are made, because of a genetic defect in the cells that eventually mature into red blood cells. This genetic defect can be present since birth or can be acquired later in life.
- Secondary: Caused by factors outside the bone marrow that trigger increased production of red blood cells

Primary erythrocytosis most often develops as a result of polycythemia vera, a type of myeloproliferative neoplasm (blood cancer) in which abnormal cells in the bone marrow produce too many red blood cells. Polycythemia vera is a slow-growing blood cancer, and therefore, many patients are only diagnosed incidentally on bloodwork and don't have symptoms at diagnosis. However, this condition can have serious complications, the most common being blood clots, and will require treatment. Monitoring this disease will become part of your routine follow up like other chronic conditions such as high blood pressure or diabetes.

Secondary erythrocytosis usually develops as a result of a disorder that increases erythropoietin secretion, a hormone made in the kidneys that stimulates red blood cell production by the bone marrow. This increased erythropoietin production can have many causes, for instance, a lack of oxygen delivered to body tissues from heart or lung disease. It is important for your doctor to look for the underlying cause of secondary erythrocytosis because there is also an increased risk of blood clots, and the treatment for secondary erythrocytosis is usually directed at treating the underlying disease.

HOW WILL MY DOCTOR FOLLOW MY CONDITION?

Your family doctor will begin with a clinical assessment and investigations (including blood work) to try and look for a cause of the erythrocytosis. Depending on what he/she suspects based on these investigations, he/she might refer you to a hematologist or another specialist for further evaluation and management.

YOU ARE ENROLLED ON AN ERYTHROCYTOSIS CLINICAL PATHWAY. WHAT DOES THIS MEAN?

The erythrocytosis clinical pathway was developed by family doctors, hematologists, and other specialists at Kingston Health Sciences Center to help with the screening and monitoring of people with erythrocytosis. 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 – Requisitions to fill out and send to lab for JAK2 testing

Ontario — Ministry of Health and Long-Term Care

Laboratory Requisition
Requisitioning Clinician / Practitioner

Laboratory Use Only — Clear Form

Name

Address

Clinician/Practitioner's Contact Number for Urgent Results

Service Date (yyyy mm dd)

Clinician/Practitioner Number | CPSO / Registration No.

Health Number | Version | Sex ☐ M ☐ F | Date of Birth (yyyy mm dd)

Check (✓) one:
☐ OHIP/Insured ☐ Third Party / Uninsured ☐ WSIB

Province | Other Provincial Registration Number | Patient's Telephone Contact Number

Additional Clinical Information *(e.g. diagnosis)*

Patient's Last Name *(as per OHIP Card)*

Patient's First & Middle Names *(as per OHIP Card)*

☐ Copy to: Clinician/Practitioner
Last Name First Name

Address

Patient's Address *(including Postal Code)*

Note: Separate requisitions are required for cytology, histology / pathology, ColonCancerCheck FIT test, and tests performed by Public Health Laboratory

x	Biochemistry
	Glucose ☐ Random ☐ Fasting
	HbA1C
	Creatinine (eGFR)
	Uric Acid
	Sodium
	Potassium
	ALT
	Alk. Phosphatase
	Bilirubin
	Albumin
	Lipid Assessment (includes Cholesterol, HDL-C, Triglycerides, calculated LDL-C & Chol/HDL-C ratio; individual lipid tests may be ordered in the "Other Tests" section of this form)
	Albumin / Creatinine Ratio, Urine
	Urinalysis (Chemical)
	Neonatal Bilirubin:
	Child's Age: days hours
	Clinician/Practitioner's tel. no.
	Patient's 24 hr telephone no.
	Therapeutic Drug Monitoring:
	Name of Drug #1
	Name of Drug #2
	Time Collected #1 hr. #2 hr.
	Time of Last Dose #1 hr. #2 hr.
	Time of Next Dose #1 hr. #2 hr.

x	Hematology
	CBC
	Prothrombin Time (INR)
	Immunology
	Pregnancy Test (Urine)
	Mononucleosis Screen
	Rubella
	Prenatal: ABO, RhD, Antibody Screen (titre and ident. if positive)
	Repeat Prenatal Antibodies
	Microbiology ID & Sensitivities (if warranted)
	Cervical
	Vaginal
	Vaginal / Rectal – Group B Strep
	Chlamydia *(specify source)*:
	GC *(specify source)*:
	Sputum
	Throat
	Wound *(specify source)*:
	Urine
	Stool Culture
	Stool Ova & Parasites
	Other Swabs / Pus *(specify source)*:

x	Viral Hepatitis *(check one only)*
	Acute Hepatitis
	Chronic Hepatitis
	Immune Status / Previous Exposure *Specify:* ☐ Hepatitis A ☐ Hepatitis B ☐ Hepatitis C or order individual hepatitis tests in the "Other Tests" section below

Prostate Specific Antigen (PSA)
☐ Total PSA ☐ Free PSA
Specify one below:
☐ Insured – Meets OHIP eligibility criteria
☐ Uninsured – Screening: Patient responsible for payment

Vitamin D (25-Hydroxy)
☐ Insured - Meets OHIP eligibility criteria: osteopenia; osteoporosis; rickets; renal disease; malabsorption syndromes; medications affecting vitamin D metabolism
☐ Uninsured - Patient responsible for payment

Other Tests - one test per line

SEE ATTACHED REQUISTION
To be done through the community access pilot for lab services

I hereby certify the tests ordered are not for registered in or out patients of a hospital.

x
Clinician/Practitioner Signature Date

Specimen Collection
Time Date

Laboratory Use Only — Print

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Hôpital Hotel Dieu Hospital
KGH Hôpital Général de Kingston General Hospital
Queen's University Faculty of Health Sciences
SEAMO Southeastern Ontario Academic Medical Organization

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Centre des sciences de la santé de Kingston

Molecular Hematology Oncology Test Requisition

Molecular Genetics Laboratory
Kingston Health Sciences Centre
76 Stuart Street, Douglas 4 Rm8-415
Kingston ON K7L 2V7
613-549-6666 x 4892 **FAX**: 613-548-1356
In house delivery tube station: # 31

Place Patient Addressograph HERE

Patient Name: _____

Date of Birth (YYYY/MM/DD): _____

Health Card Number: _____

Patient Sex: M / F / U *Version Code*

Patient Address: _____

_____

Please complete and submit accompanied by a labelled specimen, with the same two unique identifiers for testing.

Specimen Requirements	
Collection Centre:	Specimen Type:
Collection Date: (YYYY/MM/DD)	☐ Blood 3-6mL – EDTA Vacutainer
Collection Time:	☐ Bone Marrow Aspirate - EDTA Vacutainer
Collected By:	☐ Other (please specify):
For RNA tests specimen must be received within the lab within 24 hours of collection.	

Issue Report To: Authorizing Health Care Provider		
Name:		Phone Number:
Institution Address:		Fax Number:
		Authorizing Signature:
CPSO#:	OHIP Billing:	

CLINICAL HISTORY

Erythrocytosis, for JAK2 testing

DISEASE CODE	TEST REQUESTED	
☐ PMLRAR	**Diagnostic** PML::RARA Fusion t(15;17)	**RNA**
☐ FLT3NPM1	**Diagnostic**/Relapsed FLT3 & NPM1 (FLT3-ITD, FLT3-TKD, NPM1 Ex12 insertion)	DNA
☐ RT-BCR/ABL	**Diagnostic BCR::ABL** Qualitative Assessment (Major and Minor breakpoints)	**RNA**
☐ QRT BCR/ABL	**Follow-up Quantitative BCR::ABL** Breakpoint Monitoring (**p210/Major only**)	**RNA**
☐ SEND OUT	**Follow-up Quantitative BCR::ABL** Breakpoint Monitoring (**Minor**/other breakpoints) *Please include completed UHN requisition.*	**RNA**
☒ MPN	Myeloproliferative Neoplasm Panel JAK2 V617F, JAK2 Ex12, CALR Ex9, MPL W515K/L	DNA
☐ SMLP	Somatic Myeloid Lymphoid Panel; NGS, multiple gene targets (KIT included).	DNA

Please leave blank *For* **genetics** *LAB Use Only*

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Appendix D – Endnotes

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