Primary Care Management Pathway
Abnormal Lymphocyte Counts – Lymphocytosis and Lymphopenia

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 abnormal lymphocyte count pathway will help differentiate patients with high-risk features who require timely specialist assessment from those who can be safely managed by their PCP.

Absolute lymphocyte count is calculated by multiplying the total white blood cell count by the percentage of lymphocytes, with lymphocytes usually making up 20-40% of the total white blood cells (1).

For the purposes of this pathway, significant lymphocytosis is defined as an increase in absolute lymphocyte count in the peripheral blood to > 5 $x10^9$/L (1). Lymphocytosis is a common hematologic abnormality in adults with mostly reactive and sometimes malignant causes (1). The most common cause of transient lymphocytosis is an antecedent viral infection (2). Therefore, mild lymphocytosis lasting less than 3 months does not require a work-up in a well individual with no significant clinical or other laboratory changes. Other secondary causes, such as chronic infection, stress, and asplenia, tend to be driven by a polyclonal B-cell response (1, 3). Primary causes of persistent lymphocytosis in adults include Monoclonal B-cell Lymphocytosis (MBL), Chronic Lymphocytic Leukemia (CLL), or Non-Hodgkin Lymphomas (1-3). Consequently, persistent unexplained lymphocytosis requires an assessment by a medical practitioner focusing on clinical history, physical examination for lymphadenopathy and splenomegaly, a complete blood count (CBC) with differential (2).

The absolute lymphocyte count is known to decrease with age with the usual lower limit of normal being 1.5 $x10^9$/L in adulthood (4). Lymphopenia is a common occurrence, reported in 1.5-3% of CBCs (4). It is particularly common in adults aged 65 or over and usually has no clinical significance (4, 5). **Consequently, it is not recommended to investigate asymptomatic adults age 65 and over with a lymphocyte count > 0.5 $x10^9$/L.** At a chronic absolute lymphocyte count level of < 0.5 $x10^9$/L, there may be an increase in opportunistic infections (4). Younger adults with no clear etiology may be investigated when the absolute lymphocyte count is < 1 $x10^9$/L. The etiology of lymphopenia can be primary or secondary, with primary etiologies (usually primary immunodeficiency syndromes) being very uncommon in adulthood (4). Most cases of lymphopenia are secondary to infection, surgery or medication (4). HIV testing, symptoms and other laboratory features generally guide the appropriate specialty to which the patient should be referred when required (4). **In general, lymphopenia that has been asymptomatic, stable, with no other clinical findings or abnormal investigations for over 6 months does not require further investigation (4).**

Defining Significant Lymphocytosis (1-3)

- An absolute lymphocyte count of > 5 x 10^9/L
- Can have primary (neoplastic) etiology or secondary (reactive) etiology
- Blood films can demonstrate reactive lymphocytes, which seldom exceed 30 x10^9/L and vary widely in shape and size. These lymphocytes are likely to be polyclonal and related to a secondary etiology.
- Blood films demonstrating a lymphocytosis with an abnormal appearance, including lack of variation in size and shape, are suspicious for a monoclonal lymphoproliferative disorder and require further evaluation, such as flow cytometry.

Defining Lymphopenia (4-6)

- Although the lower limit of normal for absolute lymphocyte is usually 1.5 x10^9/L, the following thresholds are used to determine which asymptomatic patients require investigation:

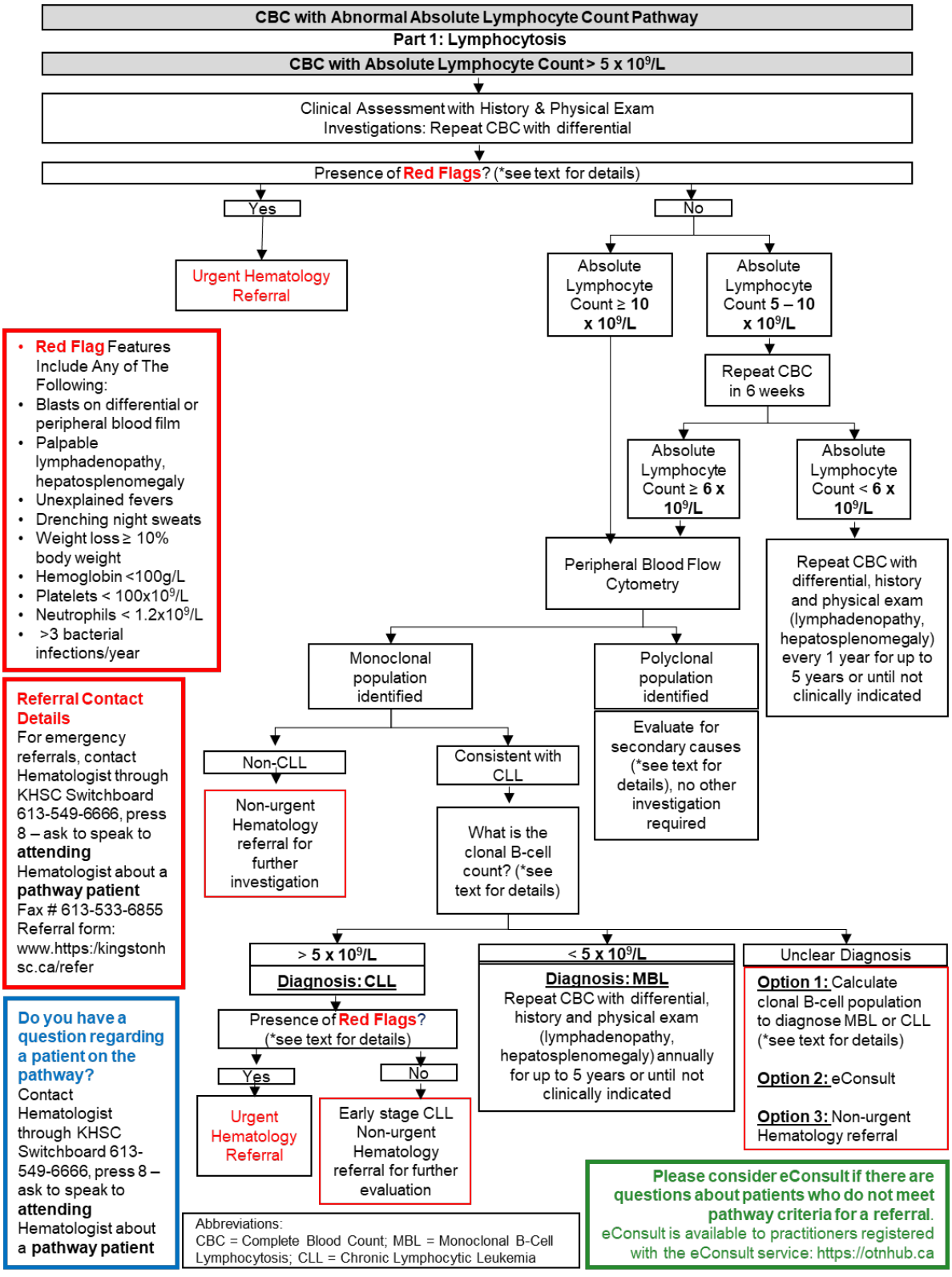
Age ≥ 65 years old and absolute lymphocyte count < 0.5x10^9/L
OR
Age < 65 years old and absolute lymphocyte count < 1x10^9/L

- Chronic lymphopenia < 0.5 x10^9/L may predispose to opportunistic infection
- Can have primary or secondary etiologies
- Primary etiologies include primary immunodeficiency syndromes which are rare in adulthood
- Age-related decreases and infection are the most common secondary causes
- HIV should be ruled out in patients with risk factors for HIV infection (such as injection drug use, and other sexually transmitted infections) and chronic lymphopenia.

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
Abnormal Lymphocyte Counts –Lymphocytosis and Lymphopenia


CBC with Abnormal Absolute Lymphocyte Count Pathway
Part 1: Lymphocytosis
CBC with Absolute Lymphocyte Count > 5 x 10⁹/L
Clinical Assessment with History & Physical Exam
Investigations: Repeat CBC with differential
Presence of Red Flags? (*see text for details)
Yes
No
Urgent Hematology Referral
Absolute Lymphocyte Count ≥ 10 x 10⁹/L
Absolute Lymphocyte Count 5 – 10 x 10⁹/L
Repeat CBC in 6 weeks
Absolute Lymphocyte Count ≥ 6 x 10⁹/L
Absolute Lymphocyte Count < 6 x 10⁹/L
Peripheral Blood Flow Cytometry
Repeat CBC with differential, history and physical exam (lymphadenopathy, hepatosplenomegaly) every 1 year for up to 5 years or until not clinically indicated
Monoclonal population identified
Polyclonal population identified
Evaluate for secondary causes (*see text for details), no other investigation required
Non-CLL
Consistent with CLL
Non-urgent Hematology referral for further investigation
What is the clonal B-cell count? (*see text for details)
> 5 x 10⁹/L
Diagnosis: CLL
< 5 x 10⁹/L
Diagnosis: MBL
Repeat CBC with differential, history and physical exam (lymphadenopathy, hepatosplenomegaly) annually for up to 5 years or until not clinically indicated
Unclear Diagnosis
Option 1: Calculate clonal B-cell population to diagnose MBL or CLL (*see text for details)
Option 2: eConsult
Option 3: Non-urgent Hematology referral
Presence of Red Flags? (*see text for details)
Yes
No
Urgent Hematology Referral
Early stage CLL Non-urgent Hematology referral for further evaluation
• Red Flag Features Include Any of The Following:
• Blasts on differential or peripheral blood film
• Palpable lymphadenopathy, hepatosplenomegaly
• Unexplained fevers
• Drenching night sweats
• Weight loss ≥ 10% body weight
• Hemoglobin <100g/L
• Platelets < 100x10⁹/L
• Neutrophils < 1.2x10⁹/L
• >3 bacterial infections/year
Referral Contact Details
For emergency referrals, contact Hematologist through KHSC Switchboard 613-549-6666, press 8 – ask to speak to attending Hematologist about a pathway patient
Fax # 613-533-6855
Referral form: www.https:/kingstonhsc.ca/refer
Do you have a question regarding a patient on the pathway?
Contact Hematologist through KHSC Switchboard 613-549-6666, press 8 – ask to speak to attending Hematologist about a pathway patient
Abbreviations:
CBC = Complete Blood Count; MBL = Monoclonal B-Cell Lymphocytosis; CLL = Chronic Lymphocytic Leukemia
Please consider eConsult if there are questions about patients who do not meet pathway criteria for a referral.
eConsult is available to practitioners registered with the eConsult service: https://otnhub.ca

CBC with Abnormal Absolute Lymphocyte Count Pathway

Part 2: Lymphopenia

CBC with Absolute Lymphocyte Count < 1 x 10^9/L

Clinical Assessment with History & Physical Exam
Investigations: Repeat CBC with differential

Presence of **Red Flags**? (*see text for details)

- Yes → Urgent Hematology Referral
- No → Repeat CBC with differential in 6 weeks

Absolute Lymphocyte Count ≥ 0.5 x 10^9/L **AND** Age > 65	Absolute Lymphocyte Count ≥ 1 x 10^9/L **AND** Age < 65	Absolute Lymphocyte Count 0.5-1 x 10^9/L **AND** Age < 65	Absolute Lymphocyte Count < 0.5 x 10^9/L **AND** Any Age
No further investigation required	No further investigation required	Clinical Assessment with History & Physical Exam	

Clinical Assessment with History & Physical Exam

Presence of **Red Flags**? (*see text for details)

- Yes → Urgent Hematology Referral
- No

HIV testing if risk factors present for HIV infection

Other investigations, treatment and consultation as clinically indicated according to patient evaluation (*see text for details)

- **Red Flag** Features Include Any of The Following:
- Blasts on differential or peripheral blood film
- Lymphadenopathy, hepatosplenomegaly
- Fevers, night sweats
- Weight loss ≥ 10% body weight
- Hemoglobin <100g/L
- Platelets < 100x10^9/L
- Neutrophils < 1.2x10^9/L
- >3 bacterial infections/year

Referral Contact Details
For emergency referrals, contact Hematologist through KHSC Switchboard 613-549-6666, press 8 – ask to speak to **attending** Hematologist about a **pathway patient**
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Do you have a question regarding a patient on the pathway?
Contact Hematologist through KHSC Switchboard 613-549-6666, press 8 – ask to speak to **attending** Hematologist about a **pathway patient**

Abbreviations: CBC = Complete Blood Count

Please consider eConsult if there are questions about patients who do not meet pathway criteria for a referral.
eConsult is available to practitioners registered with the eConsult service: https://otnhub.ca

Appendix A – Expanded Detail

What are etiologies of lymphocytosis?

Lymphocytosis is an increase in absolute lymphocyte count in the peripheral blood to > 5 $x10^9$/L (1, 7). Lymphocytosis is further described in terms of clonality. It can be monoclonal versus polyclonal by flow cytometry or molecular clonality (1, 2).

A reactive lymphocytosis is likely to be polyclonal and related to a secondary etiology. The absolute lymphocyte count rarely exceeds 30 $x10^9$/L. Lymphocytes can vary in shape and size (1, 3).

Monoclonal lymphocytosis is consistent with a primary bone marrow etiology / lymphoproliferative disorder (1-3).

The etiologies are generally divided between primary and secondary as below (1-3, 8):

- **Primary (Lymphoproliferative Disorders):**
  - Monoclonal B-cell Lymphocytosis (MBL)
  - Chronic Lymphocytic Leukemia (CLL)
  - Non-Hodgkin Lymphomas (including Mantle Cell Lymphoma, Marginal Zone Lymphoma, Follicular Lymphoma)
  - Hairy Cell Leukemia
  - Sezary Syndrome
  - Large Granular Lymphocyte Leukemia
  - Acute Lymphoblastic Leukemia
  - Adult T-Cell Leukemia Lymphoma

- **Secondary**
  - Infectious (Very Common)
    - Acute Viral Infections such as EBV, CMV, influenza, adenovirus
    - Chronic Viral Infections such as hepatitis A,B,C, HIV
    - Non-viral infections such as Bordetella Pertussis, Bartonella henselae, syphilis, malaria, tuberculosis, toxoplasma gondii, babesiosis
  - Smoking (Common)
  - Drugs/Drug Hypersensitivity Reactions such as:
    - Allopurinol, carbamazepine, or DRESS secondary to any drug
  - Autoimmune conditions
  - Other:
    - Trauma, asplenia, physiologic stress, immunization

EBV = Epstein-Barr Virus, CMV = Cytomegalovirus, HIV = Human Immunodeficiency Virus, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms

What are etiologies of lymphopenia?

Although the lower limit of normal for absolute lymphocyte is usually 1.5 x10^9/L, it is known that lymphocyte counts decrease with age (4, 5). Lymphopenia is not usually considered significant unless the absolute lymphocyte count is less than 1 x 10^9/L in those aged less than 65, or less than 0.5 x 10^9/L for those aged 65 or over (4).

The etiologies of lymphopenia can be divided into primary or secondary causes, with secondary causes significantly more common in adulthood, as below (4):

Primary (Uncommon):

- Primary immunodeficiencies with some examples including:
  - Severe combined immunodeficiency
    - Usually presents in infancy (< 1 year old) with recurrent infections and failure to thrive
  - Combined variable immune deficiency
    - Can present in adulthood with lymphopenia, recurrent bacterial infections (respiratory most common), and panhypogammaglobulinemia

Secondary (Common):

- Infections (Most Common) such as:
  - Viral including ***HIV***, hepatitis viruses, influenza, and others
  - Bacterial including tuberculosis
  - Parasitic including malaria
  - Fungal including histoplasmosis
- Medications such as:
  - Immunosuppressive agents (i.e. corticosteroids, methotrexate, azathioprine)
  - Monoclonal antibodies (i.e. rituximab)
  - Chemotherapy (i.e. fludarabine, cladribine)
- Systemic Disorders such as:
  - Autoimmune diseases (i.e. rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease)
  - Renal failure, heart failure
  - Sarcoidosis
  - Malignancies including solid organ and lymphoproliferative disorders
  - Severe malnutrition
  - Alcohol abuse
  - Radiotherapy
  - Recent surgery

HIV = Human Immunodeficiency Virus

How to approach the workup of lymphocytosis?

A significant lymphocytosis, defined as an absolute lymphocyte count of > $5x10^9$/L on CBC and differential, requires further investigation (2, 7). Flow cytometry testing has been found to be non-informative for absolute lymphocyte counts < $5x10^9$/L (9). Routine screening for CLL is not recommended (10).

The first step in evaluation is a complete history, physical exam, and review of the CBC with differential to investigate for potential etiology and to evaluate for **RED FLAGS** (see below) (1, 7). If present, **RED FLAGS** would necessitate urgent referral to Hematology.

The CBC will confirm the absolute lymphocyte count, and report abnormalities in other cell lines (1). If a peripheral blood film is reported, it may identify various morphologic features which can help determine the most likely cause. Morphologic features such as "atypical reactive" lymphocytes are suggestive of infectious mononucleosis or other viral infections (1). Other abnormal findings may include blasts (i.e. concerning for acute leukemia), "hairy cells", or small mature lymphocytes with atypically clumped chromatin consistent with MBL or CLL (1). The presence of smudge cells is non-specific on its own, and may be seen in reactive or neoplastic processes (3).

If no **RED FLAGS** are present, then investigate as follows (see Table 1 for summary) (1, 7, 11, 12):

- If the initial absolute lymphocyte count is ≥ 10 $x10^9$/L, flow cytometry is recommended to evaluate for clonality.
- If the initial absolute lymphocyte count is 5-10 $x10^9$/L, repeat the CBC in 6 weeks.
- If the absolute lymphocyte count is less than 6 $x10^9$/L on repeat CBC, then it is recommended to repeat CBC with differential, history, and physical exam (for lymphadenopathy and hepatosplenomegaly) every 1 year for up to 5 years or until no longer clinically indicated.
- If the absolute lymphocyte count is ≥ $6x10^9$/L on repeat CBC, the next step is to proceed with flow cytometry to evaluate for clonality.

Table 1

Initial Absolute Lymphocyte Count	**Action**
≥ 10 $x10^9$/L	Order Flow Cytometry
5 - 10 $x10^9$/L	Repeat CBC in 6 weeks
Repeat Absolute Lymphocyte Count	**Action**
≥ 6 $x10^9$/L	Order Flow Cytometry
< $6x10^9$/L	Repeat CBC with differential, history, physical exam (for lymphadenopathy and hepatosplenomegaly) every 1 year for up to 5 years or until no longer clinically indicated.

If the flow cytometry result shows a polyclonal population, then evaluate for possible etiologies, such as smoking, infection or autoimmune disease (see above to guide

evaluation) (2, 7). Subsequently, treatment for these conditions should be undertaken as clinically appropriate (2, 7).

If the flow cytometry identifies a monoclonal population consistent with CLL, there are 2 potential diagnoses depending on the clonal B cell count.

- If the clonal B cell count is > 5 x 10^9/L, the diagnosis is CLL.
- If the clonal B cell count is < 5 x 10^9/L AND the patient does not have lymphadenopathy, the diagnosis is MBL.
- If the flow cytometry identifies a monoclonal population that is not consistent with MBL or CLL, then Hematology referral is required for further evaluation (11, 13).

Flow cytometry results may be reported as a relative proportion, such as percent of lymphocytes or percent of total cells analyzed. The absolute clonal lymphocyte count can be calculated using the relative percentage multiplied by the pertinent population absolute count on the CBC (either absolute lymphocyte or leukocyte/WBC count).

Although many flow cytometry reports will include the number of clonal B lymphocytes, the calculation of clonal B cells and examples are included in the box below.

Calculation of Clonal B Cell Count:

Scenario 1: ***Report provides Percentage (%) Clonal B cells as Percent of Total White Blood Cell Count (more common):***

Clonal B cell Count = Percent Clonal B cells x CBC White Blood Cell Count

Example:
Patient with CBC white blood cell count of 18 x 10^9/L and Percentage clonal B cells 50% of total White Blood Cell Count on flow cytometry

Clonal B cell Count = 0.5 x 18 x 10^9/L = 9 x 10^9/L

Scenario 2: ***Report provides Percentage (%) Clonal B cells as percent of total Lymphocyte Count (less common):***

Clonal B cell Count = Percent Clonal B cells x CBC Absolute Lymphocyte Count

Example:
Patient with CBC with white blood cell count of 18 x 10^9/L, absolute lymphocyte count of 12 x 10^9/L and Percentage clonal B cells 50% of total Lymphocyte Count on flow cytometry

Absolute Number Clonal B cells = 0.5 x 12 x 10^9/L = 6 x 10^9/L

How to approach the workup of lymphopenia?

Although the lower limit of normal for absolute lymphocyte is usually 1.5 x10^9/L, the following thresholds are used to determine which asymptomatic patients require investigation (4):

Age ≥ 65 years old and absolute lymphocyte count < 0.5x10^9/L
OR
Age < 65 years old and absolute lymphocyte count < 1x10^9/L

If a patient is found to have lymphopenia by the criteria above, the first step in the evaluation includes a complete history, physical exam, review of the CBC with differential and evaluation for **RED FLAGS. RED FLAGS** would necessitate urgent referral to Hematology.

If no **RED FLAGS** are present, then a repeat CBC is recommended in 6 weeks. If the lymphopenia persists, repeat clinical assessment should be undertaken.
If there are risk factors for HIV infection, HIV testing can be pursued (4).
If the findings from the assessments above suggest an underlying cause, further investigations and treatment for these conditions should be undertaken as clinically appropriate (4). No other hematologic investigations required in absence of **RED FLAGS.**

What is Flow Cytometry Testing?

Flow Cytometry is a laboratory technology that allows for cell populations to be analyzed based on their fluorescence and light scattering patterns (14). Immunophenotyping is one of the many applications of this technology that can be used to help define a population of cells by using antibodies against certain antigens on the cell surface (CD markers) to help identify them and differentiate normal or neoplastic populations (14).

The main purposes of using flow cytometry in the context of lymphocytosis are:
1) Identify whether the lymphocytes are polyclonal (reactive) or monoclonal (neoplastic)
2) For a monoclonal population, identify specific cell surface markers to differentiate and establish a specific diagnosis (i.e. CLL vs other lymphoproliferative disorders) (7).

Please see Appendix B for how to order Flow Cytometry testing through *LifeLabs*.

What is Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL) ?

CLL/Small Lymphocytic Lymphoma (SLL) is the most common adult leukemia in the Western world with an annual incidence in Canada of 4.2/100 000, with approximately 80% of patients initially presenting in early stages of the disease (10, 15). Most cases are discovered on routine bloodwork with asymptomatic lymphocytosis (16). It is a disease of older adults with median age at diagnosis of 72 years (17, 18).

To diagnose CLL, one must have ≥5 x10^9/L **clonal** B lymphocytes in their blood with a particular immunophenotype and morphologic findings, persistent for a minimum of 3 months (15, 19). Flow cytometry is used to evaluate the monoclonality and immunophenotype of the B cells (19). On peripheral blood film, the lymphocytes are usually small, and mature with dense, aggregated chromatin, mixed in with some larger or atypical cells and prolymphocytes (17-19). Smudge cells are other findings often seen on blood film (19). Although there have been multiple recent advances in therapy and outcomes, CLL remains an incurable disease at present (15).

CLL and SLL are different forms of the same disease and are treated identically (17). In CLL there are many circulating abnormal lymphocytes in the blood, lymph nodes and bone marrow, whereas in SLL the majority of the disease is in lymphoid tissue (biopsy recommended to confirm) and blood **clonal** B lymphocytes are < 5 x 10^9/L (17, 19).

CLL is a clinically heterogeneous disease with 1/3 of patients never requiring treatment, 1/3 requiring treatment around time of diagnosis and 1/3 requiring treatment at varying lengths of time post diagnosis (20). In the context of there being significant heterogeneity in the length of time until treatment is required, many elderly patients never require treatment and die from other causes (18). Early treatment of CLL has not been shown to improve patient outcomes or survival and exposes patients to potential harms of therapy at a stage that it isn't needed (19). Therefore, the disease is managed with observation until such time that it is active enough to require therapy.

Asymptomatic early stage patients with no indications for therapy – such as progressive lymphadenopathy, hepatosplenomegaly or bone marrow failure- require only monitoring with regular complete blood counts (CBCs) every 3-12 months and physical examination to monitor for progression, which can eventually be conducted in primary care settings (2). However when there is suspicion of symptomatic or more active disease, such as progressive lymphadenopathy and hepatosplenomegaly, this warrants urgent referral to Hematology to start treatment with chemo-immunotherapeutic agents (2).

The absolute lymphocyte count is not an indication for treatment as patients are often asymptomatic despite significant elevations in the lymphocyte count (20). It should be noted that flow cytometry is only required at diagnosis. Repeat flow cytometry is not part of ongoing follow up of CLL.

What is Monoclonal B-Cell Lymphocytosis (MBL)?

The diagnosis of MBL is made when a patient has a clonal B-cell lymphocytosis <5 x 10^9/L, and is asymptomatic with no lymphadenopathy, splenomegaly, or other evidence of lymphoproliferative disorder, over a minimum 3 months (19, 21, 22).

It is estimated 3-4% of the general population has MBL with a higher incidence in family members of those with CLL (7, 18). The incidence increases with age (7) with the prevalence as high as 20% in otherwise healthy individuals above age 60 and up to 75% above age 90 (7).

MBL has subtypes based on immunophenotype: 1) CLL-type (75% of all MBL) or 2) non-CLL types (13, 21, 23).

CLL-type MBL, as the name suggests, has an immunophenotype resembling CLL (21, 23). MBL is often discovered incidentally by flow cytometry in the context of workup of lymphocytosis (21). CLL-type MBL is more common with increasing age and can be detected in > 50% of people above 95 years of age. Most CLLs are preceded by MBL, but not all MBLs will become CLL (21).

MBL is similar to monoclonal gammopathy of unclear significance in that it is a premalignant state, and is usually associated with an increase in the absolute lymphocyte count (18, 23). MBL has a rate of progression to CLL requiring treatment of 1-2% per year (18). The recommended management is a CBC, history and physical exam every 6-12 months (18, 20, 24, 25).

MBL is biologically extremely similar to early stage CLL, as the cut-off of 5 x 10^9/L was an arbitrary selection (7, 23, 24). It has been suggested that MBL and early stage CLL both share a risk of infectious complications and secondary malignancies (11, 16).

Non-CLL MBLs require evaluation by a hematologist given limited information regarding their progression and the need to investigate for a possible underlying lymphoproliferative disorder (11, 13).

I confirmed a diagnosis of Monoclonal B-Cell Lymphocytosis (MBL)/Chronic Lymphocytic Leukemia (CLL) in my patient, now what? (1, 2, 10, 20)

- Explain the diagnosis to your patient. For MBL:
  "This is a common condition that exists in the general population and becomes more common as we age. Monoclonal B-Cell Lymphocytosis is not a cancer, but it may put you at higher risk of developing a cancer that requires treatment in the future (approximately 1-2% per year). Monitoring for evolution of MBL to chronic lymphocytic leukemia requiring treatment will now become part of your routine cancer screening just like screening for colon cancer, etc."
- For CLL:
  "Chronic lymphocytic leukemia is the most common adult leukemia (a blood cancer) in the Western world and becomes more common with increasing age. The staging and requirement for treatment is dependent on several factors including numbers of lymphocytes (a type of white blood cell) in the blood, presence of symptoms (such as fever, night sweats, weight loss), and physical findings such as enlarged spleen or lymph nodes. Those with no symptoms and early disease do not require or benefit from treatment and can be safely followed with watchful waiting. 1/3 of patients never need treatment, and 1/3 will require treatment eventually in months or years. Monitoring this disease will become part of your routine follow up like other chronic conditions such as high blood pressure or diabetes. This is a condition associated with increased risk of infections, and other cancers, therefore routine immunizations, follow up of infections, and cancer screening are particularly important. You will be referred to a Hematologist to help guide further evaluation and management of this disease."
- For MBL, repeat CBC with differential and clinical evaluation with history and physical exam (particular attention for lymphadenopathy and hepatosplenomegaly) annually for up to 5 years or until no longer clinically indicated.
- For CLL with NO RED FLAGS: Please refer non-urgently to Hematology. While awaiting consultation, it would be appropriate to repeat bloodwork and clinical evaluation with history and physical exam (particular attention for lymphadenopathy and hepatosplenomegaly) every 3-6 months.
- Repeat flow cytometry is not recommended.
- Ensuring routine immunizations, and routine cancer screening of these patients is important. Annual skin surveys are particularly important, as there is an increased risk of both melanoma and non-melanoma skin cancers.
- If **RED FLAGS** arise at any time, please refer urgently to Hematology.

Investigations to conduct at diagnosis on abnormal lymphocyte count pathway if indicated (4, 10, 19)

Lymphopenia:

	Required in …
Complete blood count with differential, complete history (including for family history of primary immunodeficiency), physical examination for lymphadenopathy and hepatosplenomegaly	All
HIV testing	Patients with persistent absolute lymphocyte count < 0.5x 10^9/L or patients < age 65 with absolute lymphocyte count < 1 x 10^9/L AND Risk factors for HIV infection
Additional investigations	Dependent on presenting symptoms, clinical context, other laboratory abnormalities

Lymphocytosis:

	Required in …
Complete blood count with differential, physical examination for lymphadenopathy and hepatosplenomegaly	All
Flow Cytometry for immunophenotyping on peripheral blood	All patients with a repeat absolute lymphocyte count > 6x 10^9/L twice in 6 weeks, or single absolute lymphocyte count ≥ 10 x 10^9/L (see algorithm)
Abdominal/pelvis ultrasound	Not necessary for staging, may order if clinician concerned regarding physical exam findings for splenomegaly

Investigations to complete for follow-up on Monoclonal B-Cell Lymphocytosis (MBL)/Chronic Lymphocytic Leukemia (CLL) pathway if indicated (10, 19)

	Required in …
Complete blood count with differential, physical examination for lymphadenopathy and hepatosplenomegaly	All
Additional investigations	Those with emerging clinical indications

When should I refer my patient with an abnormal lymphocyte count to a Hematologist?

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

   ⇒ Blasts/immature or suspicious cells on differential or peripheral blood film
   ⇒ Palpable lymphadenopathy and/or hepatosplenomegaly
   ⇒ Unexplained fevers
   ⇒ Drenching night sweats
   ⇒ Weight loss ≥ 10% of body weight
   ⇒ Hemoglobin <100g/L
   ⇒ Platelets < $100x10^9$/L
   ⇒ Neutrophils < $1.2x10^9$/L
   ⇒ > 3 bacterial infections per year (requiring antibiotic treatment)

When should I stop monitoring for Monoclonal B-Cell Lymphocytosis (MBL)/Chronic Lymphocytic Leukemia (CLL)?

Guidelines currently recommend lifelong follow up for CLL(20). However, like screening suggestions in monoclonal gammopathy of unclear significance, and screening guidelines for other common cancers, it may be appropriate to consider discontinuation of follow-up in patients with a life expectancy of <5 years and among those >80 years old (26). For MBL it is considered appropriate to monitor annually for up to 5 years or until no longer clinically indicated.

When should I stop monitoring for lymphopenia?

Lymphopenia that has been asymptomatic, stable, with no other clinical findings or abnormal investigations for over 6 months does not require further monitoring or investigation(4).

Appendix B –How to Order Flow Cytometry Testing

Flow Cytometry testing is available through LifeLabs and can be ordered by primary care physicians. See sample requisition below. Green boxes must be filled by clinician to complete requisition.

LifeLabs

FLOW CYTOMETRY REQUISITION

Patient Name: HCN:

DOB: Gender:

Requesting Physician:

Name
Address
Phone#
Fax#

Patient Information Here

Clinical Information/Reason for Test:

Example: 72M with persistent lymphocytosis, please rule out monoclonal disorder.

Select a Test

Investigation of Immunodeficiency **(select only one test for investigation of immunodeficiency)**

Collected Monday – Thursday

☐ **CD4/CD8 count monitoring (TR# 788)**
For all age groups. Absolute and relative CD3, CD4, and CD8 are provided as well as CD4/CD8 ratio

☐ **Extended lymphocyte subsets for immunodeficiency (T,B,NK) (TR#3054)**
Ordered for general immunodeficiency investigation and monitoring of treatments e.g. Rituximab, Ocrevus
Panel includes CD19, CD20, CD3/CD4/CD8, CD56, CD57

Investigation of Lymphoma/Lymphoproliferative Disorder (e.g.: CLL, T-LGL, Sezary, HCL)

Collected Monday – Thursday

☒ **Lymphoproliferative disorder immunophenotyping (TR#3054)**
For investigation of suspected B-cell or T-cell lymphoproliferative disorders due to unexplained lymphocytosis – e.g.: CLL , T-LGL, Sezary syndrome,HCL

Investigation of Acute Leukemia

Collected Monday - Thursday

☐ **Acute Leukemia immunophenotyping (TR#3054)**
For investigation of suspected acute leukemia e.g. circulating blasts, unexplained cytopenias, transformation of MDS or MPN

Investigation of Paroxysmal Nocturnal Hemoglobinuria (PNH)

Collected Monday – Thursday

☐ **PNH Testing (TR#3054)**

Sample Requirements:

COLLECTION DATE AND TIME:_____

SPECIMEN TYPE:
Blood Specimen: 4 ml in EDTA (lavender top). Store and ship at 20-25°C

FOR PHYSICIAN COLLECTED SPECIMENS/NON-PERIPHERAL BLOOD:

Body Fluid Source: _____	Store and ship at 2-8°C – DO NOT FREEZE
Fine Needle Aspirate Site: _____	Store in 1mL of saline and ship at 2-8°C - DO NOT FREEZE
Tissue type: _____	Store and ship at 2-8°C – DO NOT FREEZE
Lymph node, Site: _____	Store and ship at 2-8°C – DO NOT FREEZE

CONTACT INFORMATION

For report status inquiries contact our Customer Care Centre: 1-877-849-3637
For technical inquiries contact the flow cytometry lab: 416-675-4530 Ext. 46809 OR 42096
For questions about interpretation of results contact our hematopathologists: 416-675-4530 Ext. 42040 OR 42944

Appendix C – Patient Information Monoclonal B-Cell Lymphocytosis (MBL)

PLEASE NOTE: THE FOLLOWING INFORMATION IS MEANT TO BE GIVEN TO THE PATIENT, EITHER AS A HANDOUT OR IN CONVERSATION WITH THEIR PRIMARY CARE PROVIDER.

WHAT IS MBL?

MBL stands for Monoclonal B-Cell Lymphocytosis. This is a common condition that exists in the general population and becomes more common as we age. MBL is not a cancer, but it may put you at higher risk of developing a cancer that requires treatment in the future (approximately 1-2% per year). Monitoring for evolution of MBL to chronic lymphocytic leukemia requiring treatment will now become part of your routine cancer screening just like screening for colon cancer, etc."

HOW WILL MY DOCTOR FOLLOW MY CONDITION?

Your family doctor will follow you with a clinical assessment and investigations (including blood work) every 1 year for up to 5 years or until there is a significant change in your overall health.

YOU ARE ENROLLED ON AN ABNORMAL LYMPHOCYTE COUNT (LYMPHOCYTOSIS) CLINICAL PATHWAY. WHAT DOES THIS MEAN?

The abnormal lymphocyte count (lymphocytosis) clinical pathway was developed by family doctors, hematologists, and other specialists at Kingston Health Sciences Centre to help with the screening and monitoring of people with abnormal lymphocyte counts including lymphocytosis, MBL, and CLL. 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 D – Patient Information Chronic Lymphocytic Leukemia (CLL)

PLEASE NOTE: THE FOLLOWING INFORMATION IS MEANT TO BE GIVEN TO THE PATIENT, EITHER AS A HANDOUT OR IN CONVERSATION WITH THEIR PRIMARY CARE PROVIDER.

WHAT IS EARLY STAGE CLL ?

CLL stands for chronic lymphocytic leukemia. CLL is the most common adult leukemia (a blood cancer) in the Western world and becomes more common with increasing age. The staging and requirement for treatment is dependent on several factors including numbers of lymphocytes (a type of white blood cell) in the blood, presence of symptoms (such as fever, night sweats, weight loss), and physical findings such as enlarged spleen or lymph nodes. Those with no symptoms and early disease do not require or benefit from treatment and can be safely followed with watchful waiting. 1/3 of patients never need treatment, and 1/3 will require treatment eventually in months or years. Monitoring this disease will become part of your routine follow up like other chronic conditions such as high blood pressure or diabetes. This is a condition associated with increased risk of infections, and other cancers, therefore routine immunizations, follow up of infections, and cancer screening are particularly important.

HOW WILL MY DOCTOR FOLLOW MY CONDITION?

You will be referred to a Hematologist for further evaluation and management of your disease. While awaiting your referral, your family doctor will follow you with a clinical assessment and investigations (including blood work) every 3 to 6 months.

YOU ARE ENROLLED ON AN ABNORMAL LYMPHOCYTE COUNT (LYMPHOCYTOSIS) CLINICAL PATHWAY. WHAT DOES THIS MEAN?

The abnormal lymphocyte count (lymphocytosis) clinical pathway was developed by family doctors, hematologists and other specialists at Kingston Health Sciences Centre to help with the screening and monitoring of people with abnormal lymphocyte counts including lymphocytosis, MBL, and CLL. 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 E – Endnotes

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