

About the Author



Curtis Marcoux, MD

Dr. Curtis Marcoux is an Assistant Professor at Dalhousie University and a hematologist in the Division of Hematology at Nova Scotia Health. He earned his MSc from the University of Ottawa and completed his medical training at Memorial University of Newfoundland. He pursued hematology training at Dalhousie University, followed by a fellowship in Stem Cell Transplantation and Cellular Therapy at MD Anderson Cancer Center in Houston, Texas. His clinical and research interests focus on stem cell transplantation, cellular therapies, and acute leukemia.

Affiliations: Division of Hematology, Dalhousie University, Halifax, Canada

Front-line Treatment of B-cell Acute Lymphoblastic Leukemia in Canada: Current Strategies and Evolving Paradigms

Curtis Marcoux, MD

Introduction

The treatment landscape for adults with B-cell acute lymphoblastic leukemia (B-ALL) has evolved considerably, with pediatric-inspired regimens, targeted therapies, and measurable residual disease (MRD)-guided approaches improving outcomes. However, treatment strategies in the clinic remain highly variable due to heterogeneity in prospective trials, a lack of randomized comparative data, and the continued evolution of therapies—particularly with the increasing use of targeted agents and immunotherapies in the front-line setting. The absence of national standardization further contributes to variability in clinical practice.

This review provides an overview of current front-line treatment strategies for B-ALL in Canada, highlighting key therapeutic approaches and recent advancements in optimizing care.

Front-line Treatment of *BCR::ABL1*-negative B-ALL

Multiple cooperative groups have developed front-line protocols for *BCR::ABL1*-negative B-ALL based on age, fitness, and prognostic factors.¹ However, the lack of randomized comparisons and significant heterogeneity among protocols have led to global variability, including differences among Canadian centres, without a standardized approach.

Early retrospective analyses showed superior outcomes in adolescents and young adults (AYA) treated with pediatric versus adult regimens,^{2,3} prompting prospective trials to evaluate the feasibility of pediatric regimens in adults.⁴⁻¹⁰ Although no cooperative group trials have directly randomized patients to pediatric or adult regimens, data favour pediatric-based approaches,^{11,12} which are now preferred for AYA patients at experienced centres. However, age cut-offs for 'young adults' vary widely across trials and clinical practice.

Despite becoming standard at many centres in Canada and globally, pediatric regimens present unique challenges.

Pediatric regimens are complex, incorporating multiple phases and, in some cases, risk-adapted therapy. Beyond induction, regimens are designed for outpatient administration, requiring robust clinic and day hospital infrastructure for frequent patient visits. Unlike conventional adult regimens (e.g., hyperCVAD; hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), pediatric approaches emphasize non-myelosuppressive agents such as asparaginase, glucocorticoids, and vincristine, alongside intensive early central nervous system (CNS) prophylaxis.^{4,5,9} Derived from Berlin-Frankfurt-Münster (BFM) protocols, these regimens include extended induction, consolidation, delayed intensification, and prolonged maintenance. In contrast, adult-based

protocols rely more on myelosuppressive agents like cyclophosphamide, cytarabine, and anthracyclines, with later and less frequent CNS prophylaxis.¹³ Historically, adult regimens have also incorporated allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first remission (CR1) as an intensification strategy in those at high risk of relapse. While pediatric-inspired regimens improve outcomes in AYA patients, they increase risks such as hepatotoxicity, pancreatitis, and avascular necrosis, primarily linked to asparaginase.¹² Nevertheless, the benefit-to-toxicity ratio remains favourable. CNS-directed therapy remains essential in all ALL treatment regimens.

In Canada, modified versions of the Dana-Farber Cancer Institute (DFCI) pediatric-like regimen⁵ and, less commonly, the CALGB 10403 regimen⁴ are the most frequently used for AYA patients. For older adults (>50–60 years), no

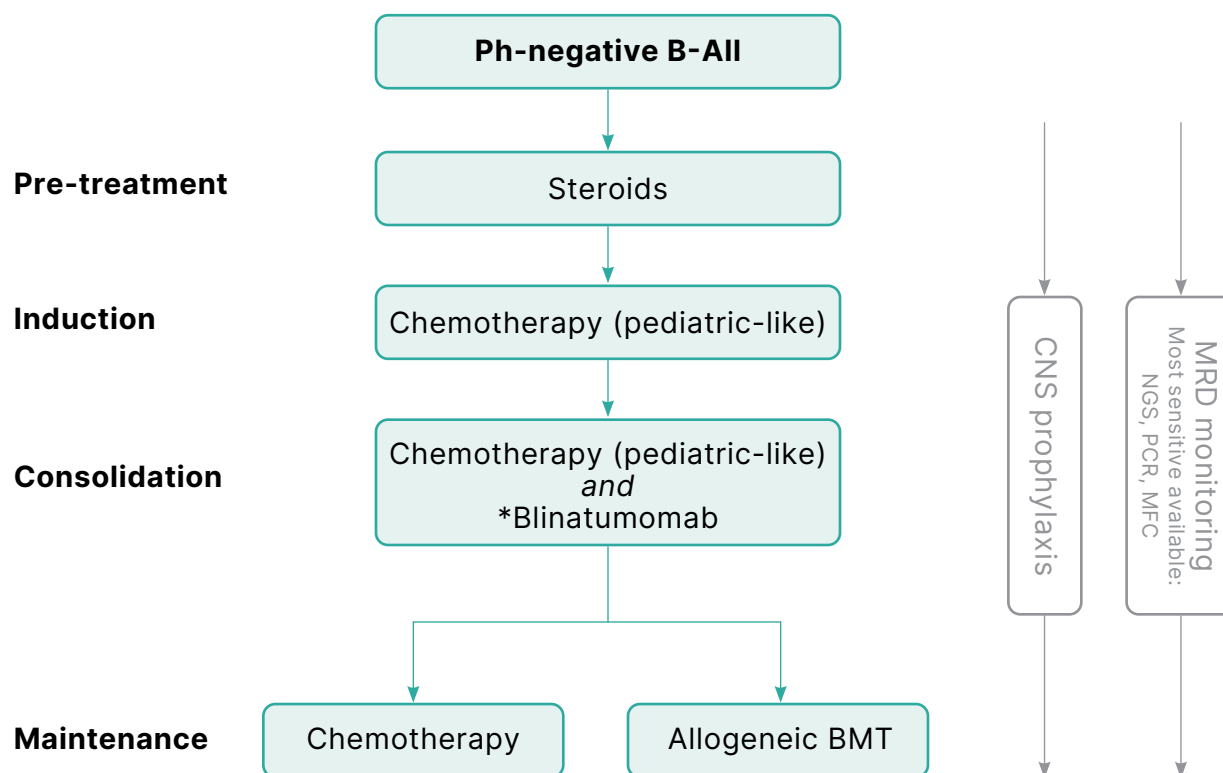


Figure 1. How I Treat *BCR::ABL1*-negative B-ALL; courtesy of Curtis Marcoux, MD

Abbreviations: BMT: bone marrow transplantation; CNS: central nervous system; MFC: multiparametric flow cytometry; MRD: measurable residual disease; NGS: next-generation sequencing; PCR: polymerase chain reaction.

* If available

standardized approach exists across Canadian centres. Some experienced centres use age-adjusted DFCl-based protocols, supported by data from the Princess Margaret Cancer Centre, where Philadelphia chromosome (Ph)-negative ALL patients aged 60–79 years had a 5-year overall survival (OS) of 40%.¹⁴ Age-adjusted hyperCVAD is another acceptable approach.¹⁵ In elderly patients (>75 years) or those with significant comorbidities or reduced fitness, palliative strategies—such as steroids, vincristine, intrathecal therapy, and maintenance with mercaptopurine and methotrexate—are often employed.

Blinatumomab, a bispecific CD19-CD3 T-cell engager, has demonstrated safety and efficacy in treating MRD ($\geq 10^{-3}$)¹⁶ and relapsed/refractory (R/R) BCR::ABL1-negative B-ALL,¹⁷ prompting interest in its use as consolidation in front-line therapy for MRD-negative patients. The ECOG-ACRIN 1910 trial, a

randomized phase 3 study in patients aged 30–70 years, compared 4 cycles of blinatumomab plus consolidation chemotherapy to chemotherapy alone in those achieving MRD-negative remission ($<0.01\%$) after induction and intensification.¹⁸ Blinatumomab significantly improved 3-year relapse-free survival (RFS) (80% vs. 64%) and OS (85% vs. 68%) over chemotherapy alone and has since become the standard of care as part of consolidation therapy in BCR::ABL1-negative B-ALL, regardless of MRD status, where available.

Blinatumomab is currently under reimbursement review by the Canadian Drug Agency for use in adult BCR::ABL1-negative B-ALL as consolidation in the frontline with multiphase chemotherapy. While not yet publicly funded, a patient assistance program is available in Canada to support access regardless of MRD status.

The Canadian Leukemia Study Group (CLSG) recently developed the CLSG ALL 1 protocol,

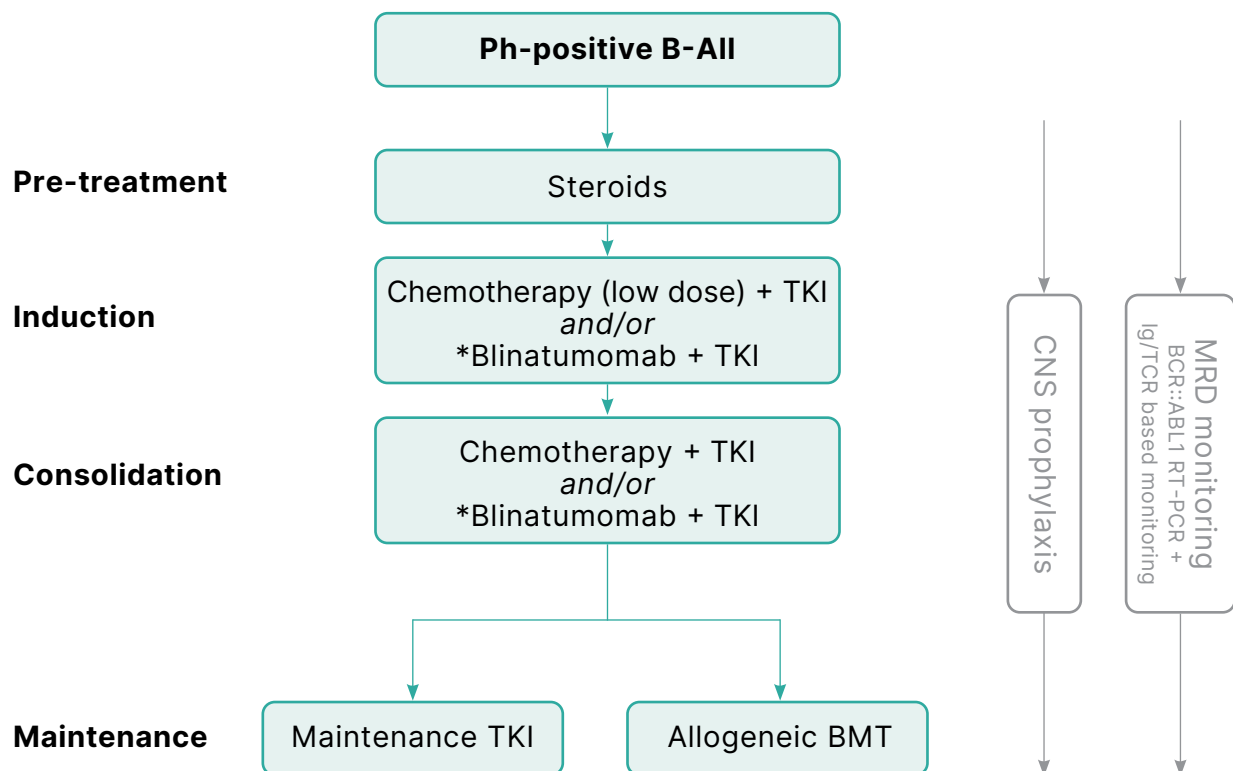


Figure 2. How I Treat BCR::ABL1-positive B-ALL; courtesy of Curtis Marcoux, MD

Abbreviations: BMT: bone marrow transplantation; CNS: central nervous system; Ig/TCR: immunoglobulin/T cell receptor; MRD: measurable residual disease; RT-PCR: reverse-transcription polymerase chain reaction; TKI: tyrosine kinase inhibitor.

* If available

integrating blinatumomab into consolidation based on a modified Princess Margaret-DFCI regimen. CLSG ALL 1 includes four MRD-independent cycles of post-induction blinatumomab and aims to reduce chemotherapy exposure, steroid use, and overall treatment duration. Key modifications include reducing intensification to seven cycles across all age groups, eliminating methotrexate from intensification, and shortening maintenance to 18 cycles. Regular MRD assessments are recommended to validate the CLSG ALL 1 approach, clarify the role of transplant, and inform future treatment refinements. My approach to the upfront treatment of *BCR::ABL1*-negative ALL is shown in **Figure 1**.

Front-line Treatment of *BCR::ABL1*-positive B-ALL

Ph-positive B-ALL, the most common genetic subtype of B-ALL, occurs in 25%–30% of cases, with incidence increasing with age.¹⁹ It arises from the t(9;22) translocation, resulting in *BCR-ABL1* oncoprotein expression and constitutive kinase activation. Previously associated with poor survival, the introduction of tyrosine kinase inhibitors (TKIs) and sensitive MRD monitoring has markedly improved outcomes.

BCR::ABL1-positive ALL exhibits reduced chemosensitivity with remissions often being short-lived even in patients achieving a complete response (CR).^{20,21} Historically, allo-HSCT was recommended for all eligible patients with suitable donors, though long-term survival rates remained low.^{22,23} The introduction of TKIs has transformed treatment, with imatinib combined with low-dose chemotherapy inducing CR rates exceeding 95%, reducing induction-related mortality, and achieving survival outcomes comparable to standard induction therapy.^{24,25} Second-generation TKIs (e.g. dasatinib, nilotinib) have further improved efficacy and proven safe in combination with chemotherapy.^{26–30} Though indirect comparisons suggest these agents may be superior to imatinib, no front-line randomized trials have established a definitive standard. The only randomized data come from a pediatric study (median age 7.8 years), where dasatinib combined with intensive chemotherapy significantly improved 4-year event-free survival (EFS; 71.0% vs. 48.9%) and OS (88.4% vs. 69.2%) while reducing the 4-year cumulative risk of isolated CNS relapse (2.7% vs. 8.4%) compared to imatinib.³¹

The acquisition of the T315I mutation is a key mechanism of relapse in patients treated with first- and second-generation TKIs, driving interest in the front-line use of ponatinib, a third-generation TKI with activity against *ABL1* mutations including T315I.^{32–34} The recent PhALLCON trial randomized newly diagnosed patients with Ph+ ALL to ponatinib versus imatinib with reduced-intensity chemotherapy, demonstrating significantly higher MRD-negative CR ($\leq 0.01\%$ *BCR::ABL1*) rates with ponatinib (34.4% vs. 16.7%) and a trend toward improved EFS.³⁵ Long-term survival data are awaited to determine whether these findings translate into a survival benefit. Based on current evidence, second- or third-generation TKIs are preferred for front-line therapy, though imatinib remains a reasonable option where access to newer agents is limited. Finally, dual *BCR::ABL1* inhibition with asciminib—an allosteric *BCR::ABL1* inhibitor targeting a distinct site from ATP-competitive TKIs—and dasatinib has shown promise in a phase 1 study. However, further research is needed to determine the safety and efficacy of dual TKI therapy relative to current standard treatments.³⁶

Given the success of blinatumomab in MRD eradication¹⁶ and treatment of low-level disease in R/R B-ALL,³⁷ there was interest in evaluating its role as a consolidation therapy in *BCR::ABL1*-positive B-ALL. The GIMEMA LAL2116 (D-ALBA) study evaluated dasatinib and prednisone induction followed by 2 to 5 cycles of blinatumomab consolidation in newly diagnosed Ph-positive B-ALL.³⁸ Nearly all patients (98%) achieved complete hematologic response after chemotherapy-free induction, with 29% achieving molecular remission (MR), defined as undetectable or non-quantifiable *BCR::ABL1*. MR rates increased to 60% and over 80% after 2 and 4 cycles of blinatumomab, respectively. Similarly, ponatinib, when used either concurrently^{39,40} or sequentially⁴¹ with blinatumomab, has demonstrated safety and efficacy, leading to high rates of deep molecular responses. While CNS prophylaxis is a standard component of ALL therapy, particular attention is needed in chemotherapy-free regimens, as CNS relapse remains a common pattern of disease recurrence. Further, patients with the IKZF1Plus genotype (*IKZF1* deletion alongside deletions in *CDKN2A/B* and/or *PAX5*) remain at high risk of relapse.⁴⁰ Notably, blinatumomab is not currently available in Canada outside of clinical trials for front-line *BCR::ABL1*-positive ALL. My approach to

the upfront treatment of *BCR::ABL1*-positive ALL is shown in **Figure 2**.

Additional Considerations: CNS Prophylaxis

There is a paucity of data on CNS-directed therapy in adult ALL, leading to variability in clinical practice. The first lumbar puncture (LP) is typically performed at the time of the first scheduled intrathecal (IT) chemotherapy unless neurological symptoms warrant earlier evaluation. Whether LP should be delayed until circulating blasts clear remains debated due to the theoretical risk of CSF contamination.

Adult ALL regimens include CNS-penetrating systemic agents (e.g., dexamethasone, pegaspargase, methotrexate, 6-mercaptopurine, cytarabine, dasatinib) alongside IT chemotherapy for prophylaxis. Standard regimens for CNS-negative patients historically include 8–12 IT treatments, but with the incorporation of immunotherapies (e.g., blinatumomab) and reduced-intensity chemotherapy, CNS prophylaxis has become increasingly important. Modern regimens now incorporate upwards of 15 IT treatments. Adherence to established treatment protocols for CNS-directed prophylaxis is essential to ensure adequate protection against CNS relapse. Notably, most adult protocols do not include radiotherapy for patients without CNS involvement at diagnosis.

Indications for Transplant in First Complete Remission

Allo-HSCT remains a critical therapeutic strategy for high-risk ALL, particularly when standard chemotherapy alone is unlikely to provide durable disease control.⁴² Advances in targeted therapies and MRD-driven treatment strategies have improved survival rates, and indications for allo-HSCT in first complete remission (CR1) continue to evolve, balancing the risk of relapse against transplant-related morbidity and mortality.

BCR::ABL1-negative B-ALL

Among Ph-negative B-ALL subtypes, Ph-like, *KMT2A*-rearranged (*KMT2A*-r) ALL and those with complex karyotype remain particularly challenging due to high relapse rates and poor responses to conventional chemotherapy. Ph-like ALL, defined by a gene expression profile similar to Ph-positive ALL but lacking *BCR::ABL1*,^{43,44} is associated with

inferior survival outcomes with chemotherapy alone. However, routine identification of Ph-like ALL remains limited in many centres due to the lack of widely available, standardized diagnostic assays. Data from GIMEMA,^{45,46} MD Anderson,⁴³ and City of Hope⁴⁷ suggest that allo-HSCT improves outcomes, particularly in MRD-positive patients, with post-transplant survival rates comparable to other Ph-negative subtypes. Further, a recent U.S. multicentre study found that, despite higher induction failure in Ph-like ALL, progression-free survival (PFS) and OS after allo-HCT in CR1 were similar to other Ph-negative subtypes.⁴⁸

Similarly, *KMT2A*-r ALL has historically carried a poor prognosis, though data from MD Anderson⁴⁹ and the GRAALL⁵⁰ support the benefit of allo-HSCT in this subgroup. However, emerging evidence suggests that a subset of *KMT2A*-r patients with early MRD-negativity and favourable molecular features may achieve durable remissions without transplant.⁵¹ Complex karyotype (≥ 5 abnormalities) and low hypodiploidy (30–39 chromosomes)⁵² are both high-risk cytogenetic abnormalities and should prompt early referral for allo-HSCT.

As targeted therapies,^{53,54} immunotherapies,¹⁸ and refined MRD-based risk stratification⁵⁵ continue to advance, the role of allo-HSCT in these subtypes may evolve. For now, it remains a key consideration for eligible patients in CR1.

BCR::ABL1-positive B-ALL

The role of allo-HSCT in *BCR::ABL1*-positive ALL has evolved significantly. Before the introduction of TKIs, transplant was the standard of care for all eligible patients, supported by donor versus no-donor analyses demonstrating superior outcomes.^{20,23} In the TKI era, studies have continued to support the benefit of consolidative allo-HSCT with first or second-generation TKIs;^{29,56–58} however, these studies did not routinely incorporate MRD-guided risk stratification into transplant decisions.

Recent evidence suggests that patients achieving early, deep remissions with TKI-based therapy may safely forgo allo-HSCT. Prospective trials of imatinib²⁴ and nilotinib-based⁵⁹ regimens found no survival advantage for transplant in MRD-negative patients. Similarly, a U.S. multicentre study reported no OS benefit for allo-HSCT in patients achieving complete molecular remission (CMR) within 90 days of diagnosis, as higher non-relapse mortality (NRM) offset lower relapse rates in those undergoing transplant.⁶⁰ Although

not yet routinely available in Canada for front-line therapy, ponatinib has shown efficacy in inducing deep and durable remissions without allo-HSCT. A single-centre study of ponatinib and hyperCVAD reported CMR rates exceeding 80%,³² with only 23% of patients undergoing allo-HSCT in CR1 and a 6-year OS of 87% in those not transplanted.^{32,61}

The necessity of transplant is further challenged by the emergence of highly effective low-intensity or chemotherapy-free regimens incorporating blinatumomab. The GIMEMA LAL2116 (D-ALBA) trial, which combined dasatinib with blinatumomab, reported a 98% CR rate, with the majority achieving MRD-negative remissions.^{38,62} Sustained remissions were observed in nearly all MRD-negative patients without transplant, whereas MRD-positive patients undergoing allo-HSCT experienced low transplant-related mortality. Ponatinib combined with blinatumomab may further improve these outcomes, as an MD Anderson study of concurrent ponatinib and blinatumomab reported next-generation sequencing (NGS)-MRD negativity in 98% of patients, with only 3% requiring transplant and a 3-year OS of 91%.^{39,40} An interim analysis of the GIMEMA ALL2820 trial, a follow-up to LAL2116 in which dasatinib was replaced with ponatinib, demonstrated similarly impressive results.⁴¹ Although the median follow-up was just over 6 months, the estimated 12-month disease-free survival and OS were 95.6% and 94.9%, respectively. Transplant allocation was based on the presence of the *IKZF1*plus genotype and MRD persistence, with only 12% of patients undergoing allo-HSCT. The GRAAPH-2024 study (NCT06860269) aims to clarify the role of transplant by randomizing patients in CMR after treatment with ponatinib, blinatumomab, and low-intensity chemotherapy to either allo-HSCT or continued TKI-based therapy.

Measurable Residual Disease

MRD is a key predictor of relapse and a critical determinant in transplant decisions for both Ph-negative and Ph-positive ALL, often outweighing traditional clinical and genetic risk factors.⁶³⁻⁶⁶ Across multiple risk stratification models, MRD is the most consistent factor guiding allo-HCT in CR1,⁶⁷ with transplant offering a survival advantage in MRD-positive patients.^{68,69} The necessity of allo-HSCT in MRD-negative high-risk patients remains uncertain, particular when highly sensitive methods of MRD detection (NGS-MRD) are used. In BCR-ABL1-positive

ALL, reverse transcription-polymerase chain reaction (RT-PCR) for *BCR::ABL1*, though widely used, is less sensitive and correlates poorly with immunoglobulin (Ig)/ T cell receptor (TCR) PCR and NGS-based MRD.^{70,71} NGS-MRD can identify patients with a "CML-like" profile, where residual *BCR::ABL1* transcripts do not necessarily indicate active disease.⁷¹ Given the limited access to NGS-MRD in Canada, the most sensitive assay available should be used for *BCR::ABL1*-negative ALL, while in *BCR::ABL1*-positive ALL, quantitative PCR for both p190 and p210 ABL1 transcripts, ideally alongside Ig/TCR-based assays, is recommended to guide transplant decisions. Ongoing evaluation of MRD dynamics and treatment-specific thresholds remains crucial as front-line therapies evolve.

Conclusion

Despite significant advances in B-ALL treatment, challenges persist, particularly the absence of standardized guidelines and disparities in access to novel agents such as blinatumomab and ponatinib. The expanding role of targeted and immunotherapies, including chimeric antigen receptor (CAR)-T cell therapies and next-generation TKIs, is reshaping treatment paradigms and necessitating a reassessment of transplant indications. Moving forward, harmonizing treatment strategies and refining risk-adapted approaches will be crucial to optimizing outcomes across diverse clinical settings.

Correspondence

Curtis Marcoux, MD

Email: Curtis.Marcoux@nshealth.ca

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