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## Delays in referral and diagnosis for chronic hematologic malignancies: A literature review

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### Abstract

To better understand the extent of diagnostic and referral delays from primary care providers (PCPs) for chronic hematologic malignancies, causes of these delays, and their possible effects on cancer outcomes, an extensive review of the literature was performed. Over 50 studies were reviewed, including many that concern delays in referral and diagnosis for solid tumors, as there was only sparse literature on delays specific to the liquid tumors. Delays for some chronic hematologic malignancies have been documented, mainly in centralized health care systems. Possible reasons for delays include PCPs' lack of exposure to hematologic malignancies, limited knowledge of associated signs and symptoms, and a reliance on patient symptoms to prompt referral (as opposed to signs and screening). Patient characteristics such as age, gender and race-ethnicity are also likely to play a role, although it is unclear if these exert their effect primarily via patient or provider mechanisms. Unfortunately, the outcomes associated with such delays are largely unreported, possibly because delay is complex to define and difficult to measure.

**Keywords:** Hematologic malignancy, delays, diagnosis, referral, primary care provider; lymphoma and Hodgkin disease, neoplasia, myeloid leukemias and dysplasias

### Introduction

The primary care provider (PCP) is frequently the first point of medical contact for patients with malignancy, and as such, serves a critical role in facilitating cancer diagnosis and treatment. Although guidelines for screening common malignancies such as breast, colon and cervical cancer help in this effort, hematologic malignancies are comparatively rare and often present with subtle signs and symptoms. Consequently, they pose a unique problem for the PCP. This is especially true of the chronic hematologic malignancies such as chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), multiple

myeloma (MM) and certain indolent types of non-Hodgkin lymphoma (NHL).

Concerns about delays in diagnosis and referral for cancer patients are not new. An early (1974) descriptive study using interviews with cancer patients and their families defined just three steps considered to be the 'ideal' pathway for patients to attain definitive oncologic care; some patients experienced excessive delays, defined as one or more extra steps (e.g. referral to an additional clinical expert) [1]. A later descriptive work by Richard Wender categorised barriers to optimal cancer detection by PCPs into three categories: 'practitioner-based' (e.g. lack of knowledge, financial disincentive to refer), 'patient-based' (e.g. fear about seeing physician, financial barriers to

receiving care), and 'health care system-based' (e.g. lack of specialists, lack of government support) [2].

Whatever the source of delay, timeliness of care has become a priority, and was identified as one of six aims of quality improvement in the Institute of Medicine's 2001 *Crossing the Quality Chasm* report [3]. The report identified significant delays in all aspects of care delivery, including access to appointments, prolonged responses to diagnostic findings, and overdue implementation of therapeutic interventions. The literature regarding solid tumors has indeed documented delays in referral and diagnosis for many cancers in both children and adults [4–9], linking them to the frequency of cases experienced by PCPs in clinical practice [10–13], as well as deficits in knowledge regarding screening and diagnosis [12,14]. In addition, delays in referral and diagnosis have been shown to have a possible negative effect on the outcomes associated with some solid tumors [15,16]. In contrast, little research has focused on hematologic malignancies, despite the fact that improved techniques for pathologic diagnosis, staging, prognostication and therapy may translate into significant benefits for patients who are referred and diagnosed in a timely manner.

Our aim was to describe a possible problem regarding referral and diagnosis of patients with hematologic malignancies. We focused on the chronic hematologic malignancies, as we reasoned that their insidious nature would make them the most susceptible to significant delays. We also aimed to determine what is known about how such delays might affect disease-related outcomes, as well as present a sample of findings regarding the etiology of delays for two common solid tumors (breast and colon) and suggest how these factors may or may not manifest for chronic hematological malignancies. Finally, we aimed to present a research agenda for further study informed by our literature review.

## Methods

To identify relevant articles, we searched the PubMed, EMBASE and Social Sciences Citation Index databases. Search terms used included: *anemia, breast cancer, colon cancer, delayed diagnosis, diagnostic delay, family physician, general practitioner, hematologic malignancies, leukemia, lymphadenopathy, lymphoma, multiple myeloma MM, myelodysplasia, pancytopenia, presentation of cancer, primary care physician, referral patterns, splenomegaly* and alternate synonyms in various combinations. We also searched the abstracts presented at the most recent three meetings of the American Society of Hematology. We first used the subject headings in each database followed by keyword searches. Promising abstracts

were reviewed, and a subset of those were retrieved for in-depth review (read in their entirety by one or more authors). Several articles were also selected to undergo second-order searches for relevant publications through their references cited. Our initial search strategy yielded 144 studies possibly relevant for inclusion; upon detailed review, 56 of these were deemed appropriate to include in this manuscript. Although few studies assessed barriers to referral and diagnosis specifically for the hematologic malignancies, several addressed such barriers for solid-tumors, as well as factors limiting PCPs' practice of cancer prevention and screening. Of note, no study specifically addressed these topics for CLL or MDS.

## Findings from literature review

### *Delays in diagnosis and referral for hematologic malignancies*

An important issue with all studies of delays in diagnosis and referral is how 'delay' is conceptualised, especially given the diverse and complex pathways that patients take to treatment [17]. For example, delays can occur due to patients' failure to see a provider in a timely manner, providers' failure to quickly refer patients to specialists, and specialists' failure to quickly administer treatment; each of these types of delay is likely to have its own covariates [18]. In addition, the way that delay is measured can certainly affect outcomes, as very different assessments of delay may be attained through surveying physicians, surveying patients, reviewing medical records or utilising large databases. Different assessments can further be confounded by issues such as recall bias and quality of documentation [9]. Finally, the time period that is considered an unacceptable delay is variable (e.g. from 2 weeks to 3 months) [15] and can affect how delays interact with outcomes.

In addition, making comparisons between delays for different cancers can be difficult, unless several tumor types are presented in the same study. To that end, a series of manuscripts has analysed data from the United Kingdom's National Health Service (NHS) regarding delays in diagnosis for patients with six cancers including NHL [9,19,20]. The total duration of diagnostic delay (defined as first symptom until definitive diagnosis) varied by cancer, with breast cancer patients experiencing the shortest mean delay (55 days), NHL patients falling in the middle (103 days) and prostate cancer patients experiencing the longest delay (149 days). The authors concluded that the comparatively straightforward presentation of a disease such as breast cancer may combine with an increased public awareness of the same to lead to comparatively shorter delays.

In the NHS study, patients who saw their PCP prior to diagnosis experienced longer delays than those who presented directly to a specialist [9,19]. In a subsequent analysis of the entire cohort of patients [20], longer delays were experienced by women, younger patients, those with lower socioeconomic status, those who were of black or south Asian descent, and those who were unmarried. Most of these patient factors had no apparent effect on diagnostic delay for patients with NHL, except age; those NHL patients younger than 25 and over 75 years old experienced total delays of 63 and 85 days, respectively, whereas NHL patients 45 to 54 years old experienced a total diagnostic delay of 128 days.

In another British study (retrospective chart review) review of delays in diagnosis and treatment for 89 NHL patients presenting to a regional hospital, 'patient delay' (symptom onset to time patient sought medical advice) accounted for the most time passed between symptoms and treatment (a mean of 3.9 months), compared with 'diagnostic delay' (time from seeking medical advice to time of diagnostic biopsy, 2.8 months), and 'treatment delay' (diagnostic biopsy to start of treatment, 1.2 months) [21]. Delays were not affected by the location of treatment clinic or by NHL subtype. A more recent chart review of 194 British NHL patients showed that on average, over a year elapsed between the onset of symptoms and the beginning of treatment [22]. Here, delays to treatment did vary by lymphoma type, as patients with more aggressive disease (e.g. diffuse large B-cell lymphoma) experienced shorter delays than those with more indolent disease (e.g. follicular lymphoma).

A retrospective study of 116 Canadian patients with NHL yielded an average of 137 days from the onset of symptoms to start of treatment, with the time before diagnosis constituting the largest proportion of total delay. Males and patients with symptomatic 'B-symptoms' (i.e. fever, weight loss and night sweats) had shorter delays. Patients in middle age groups experienced longer delays than patients on either extreme of the age spectrum. For all patients, once a diagnosis was made, only 18 days passed before the initiation of treatment, compared with 110.5 days from symptom onset to pathologic diagnosis [23].

Interestingly, although the above literature documents significant delays in diagnosis for some hematologic malignancies, not all studies argue that PCPs should be more aggressive with regard to referral. A Dutch retrospective chart review of 82 patients who presented to their PCPs with lymphadenopathy found that although PCPs referred 90% of patients ultimately found to have malignancy within

4 weeks, a high proportion of patients with benign disease (68%) were also referred within 4 weeks. The authors suggested that PCPs should be less liberal with referrals because benign cases were being referred nearly as often as malignant cases [24].

On the other hand, presentation for chronic hematologic malignancies can be subtle, and determining the appropriate level of suspicion can be difficult. In a retrospective chart review of 1027 patients diagnosed with MM, patients often presented with non-specific signs and symptoms such as anemia (73%), anemia-related fatigue (32%) and weight loss (24%) [25]. In a Dutch population-based registry of 127 patients with MM [26], the disease was not part of the initial differential diagnosis for 37% of patients; yet, of those, 51% had advanced disease (stage III) at diagnosis, suggesting that the absence of symptoms does not imply early-stage disease. Interestingly, a recent analysis of patients with MM in the Surveillance, Epidemiology, and End Results (SEER) registry, from an analytic sample of 5185 patients, found that patients with higher comorbidity had a higher adjusted likelihood of diagnostic delay [defined as greater than the median time (98 days) between initial claim for anemia or back pain], perhaps representing the difficulty of diagnosing patients with non-specific symptoms in the setting of substantial comorbidity (OR 1.17, 95% CI: 1.03–1.33) [27].

Like MM, CML can also present with subtle signs and symptoms. A review of the records of 430 patients with CML who had undergone allogeneic bone marrow transplantation found that 20% were diagnosed incidentally, as a result of a routine blood test or due to the discovery of splenomegaly on routine physical examination [28]. In another review of 341 CML patients, 40% of those diagnosed after 1985 were asymptomatic at the time of diagnosis compared with less than 20% diagnosed before that time [29]. Such increases in asymptomatic diagnoses may be the result of an increased use of routine blood tests in current practice, but begs the question: does detecting patients earlier improve disease-related outcomes?

#### *Do referral and diagnostic delays for chronic hematologic malignancies affect outcomes?*

For malignancies such as colon and breast cancer, a delay in referral has been shown to lead to the diagnosis of a more advanced stage of cancer [15,16,30–33], but whether or not this translates to worse outcomes is less clear [15,30,33–36]. The ultimate effects of delays in diagnosis are even less understood for the hematologic malignancies. Studies that specifically assess the outcomes associated

with diagnostic delays for this population are rare, perhaps because lack of swift diagnosis and expeditious treatment for aggressive malignancies such as acute myeloid leukemia and Burkitt lymphoma are known to lead to rapid death. Given the many tasks PCPs are already expected to perform, it will be difficult to motivate them to be more vigilant about surveillance for and diagnosis of chronic hematologic malignancies without clear evidence that early diagnosis saves lives (such as that which exists for several other types of cancers) [37–39].

A few studies provide preliminary insight. First, in a review of 50 Norwegian patients with Hodgkin lymphoma (HL) treated between 1985 and 1993, a median of 4 months was found to have elapsed between the first symptoms of HL and histological or cytological confirmation [40]. Within 6 months, 78% of cases had a verified diagnosis, and there was no relationship between delay in diagnosis and stage of disease, relapse rate, or overall survival. Second, especially for indolent NHL, an upfront ‘watch and wait’ strategy is often appropriate, and may thus diminish the value of rapid referral and diagnosis. Indeed, a review of 92 patients with low-grade NHL found that those whose treatment was intentionally delayed at diagnosis experienced the same survival as those who received immediate treatment [41]. On the other hand, a recent case review of 92 patients with MM showed that a prolonged time to diagnosis (duration of symptoms > 6 months) had a significant effect on disease-free (but not overall) survival ( $p = 0.043$ ) [42].

#### *Delays in referral and diagnosis for solid tumors: Lessons for the hematologic malignancies*

As PCPs are responsible for requesting specialist consultation for patients with suspected malignancy, it is important to understand the factors that influence their referral behavior. Although cancers are often first noticed when patients present with symptoms [11,43], with aggressive screening, it stands to reason that PCPs can find more asymptomatic cases [11]. Still, a large number of referrals for oncologic genetic testing and counseling are patient driven [44], and referrals from PCPs often do not meet criteria established by expert panels for screening and referral [44,45].

PCPs’ oncology knowledge may be inadequate. For example, an Italian survey of 134 family doctors, 31 general surgeons and 33 internists utilising treatment vignettes found that less than half of the physicians surveyed selected appropriate adjuvant chemotherapy for colon cancer or any chemotherapy as first-line treatment for small-cell lung cancer [12]. One might expect PCPs to be even less able to diagnose and manage hematologic malignance given their rarity;

indeed, in a recent American survey of 357 PCPs, only 22% said that they were confident educating patients about hematologic malignancies, and only 10% reported having ordered blood tests for monoclonal gammopathy of undetermined significance (MGUS) and MDS [46]. In recent years, there has been remarkable growth in prognostic indicators and therapeutic options for patients with chronic hematologic malignancies, and PCPs’ lack of awareness of these advances may also affect timeliness of referral.

PCPs sometimes have unfounded confidence in their abilities to detect cancer. In a study of ovarian cancer screening, 56% of PCPs felt qualified to interpret genetic test results despite ‘considerable variability’ in a standardised assessment of their understanding of common risk factors [47]. In addition, although one would expect a perceived lack of familiarity with cancer diagnoses to be associated with timely referral, this relationship is not always consistent. For example, despite reporting rare exposure to melanoma, 60% of surveyed PCPs rarely or never referred patients with suspicious pigmented lesions to specialists, preferring to excise such lesions themselves [13]. Finally, beyond actual or perceived knowledge, other PCP factors may play a role. As an example, one study found that PCPs reviewing hypothetical lung cancer vignettes were most likely to suspect malignancy when patients experienced clinical deterioration, had family members who insisted on consultation, or when another primary care colleague provided an informal opinion suggesting referral [48].

The literature regarding solid tumors also suggests that PCPs are more likely to refer patients to specialists in the presence of abnormal symptoms rather than abnormal signs, laboratory results or imaging. For example, a prospective study of 159 Italian PCPs found that patients referred for colonoscopy were at least twice as likely to have reported abdominal pain and bloating than to have had laboratory evidence of iron deficiency anemia, even though the latter was much more predictive of colon cancer [49]. Likewise, a review of surgical referrals for colorectal cancer in the United Kingdom showed that although delays from symptoms to surgical treatment improved between 1978 and 1988 overall, the improvement was minimal for patients with right-sided cancer [50]. This may be because right-sided disease is traditionally more difficult to diagnose due to fewer symptoms and more subtle presentation (such as isolated mild anemia).

In breast cancer, patient symptoms may also lead to quicker referral. In a cohort of 146 patients with suspicious breast lesions, the mean time between awareness of diagnostic need and completion of diagnosis was 68.4 days for women with palpable masses compared with 71.9 days for those referred

due to an abnormal mammogram [8]. Similarly, at a London breast clinic, compared with those without, women with breast lumps experienced less patient delay as well as 'system delay,' defined as the time between a women's first medical contact and her first consult with a breast specialist [51].

The above literature regarding symptoms and signs for solid tumors has potential relevance to patients with chronic hematologic malignancies. It might follow that patients with hematologic malignancies who exhibit only mildly abnormal laboratory results but no obvious symptoms might be less likely to be referred to specialists than patients with no abnormal laboratory results but symptoms suggestive of malignancy (e.g. night sweats, fever, or palpable lymph nodes). Such PCP behavior may ultimately make sense, as patients with chronic hematologic malignancies who are asymptomatic may do well without treatment despite their laboratory abnormalities; however, it also may be true that patients with hematologic malignancies who are diagnosed in the setting of obvious symptoms respond less well to treatment (e.g. MM patients with bone fractures).

PCPs may also be influenced by patient demographic characteristics, although when delays are associated with these characteristics, it is uncertain if they are ultimately due to patient or provider effects. For example, patient insurance status has been correlated with delays in cancer diagnosis for young adults and older adolescents with cancer [52], but whether the delay stems from patient or physician behavior is unclear. A German study of rectal cancer patients found that patients on welfare had greater treatment delays (399 days) as compared with those with supplemental insurance (107 days), with patient delay (first symptoms to first physician contact) comprising the majority of the total delay [53]. Whether such delays for patients of lower socioeconomic status are primarily due to patient delays in seeking care (due to issues such as access to transportation or inability to miss work) or PCP delays in arranging care is unclear; however, it is reasonable to assume that such factors may also play a role in referral for patients with chronic hematologic malignancies.

Other patient factors such as age, sex, race-ethnicity and education may act as covariates of the likelihood of referral [18,54,55]. For example, in a population-based study using data from the SEER registry, African-American women, compared with Caucasian women, had a longer diagnostic delay (time from initial consult to biopsy confirming the diagnosis), and represented the population with the highest proportion having a delay of over 2 months [56]. In the same registry, most women, regardless of race, were treated within 3 months of their first

medical contact; however, a greater proportion of African-American women had a delay of more than 3 months before start of treatment compared with their Caucasian counterparts (22.4% vs. 14.3%, respectively) [57]. The effect of race-ethnicity on breast cancer referral and diagnostic delay has not been uniformly observed, however [36,54], and its possible role in delays for hematologic malignancies is currently unknown.

A patient's fear of being diagnosed or having to undergo a diagnostic test may also cause delays in referral or diagnosis. For example, one group found that the majority of delays in colon cancer diagnoses took place between the onset of patient symptoms and PCP office visit (112 days) [49]. The time between PCP visit and colonic investigation was considerably shorter (16 days), suggesting that patient delay may constitute the most significant factor contributing to referral and diagnostic delay. Indeed, another study of colorectal cancer patients found that 50% reported fear of an unpleasant investigation as a major reason for not seeing their PCP sooner [53]. How such results may be applied to patient delays for hematologic malignancies is uncertain, because, given their rarity, most patients are unlikely to be aware of the diseases' associated signs, symptoms and diagnostic procedures.

#### *Areas for further research*

Our review identified few studies that examined delays in referral or in diagnosis for chronic hematological malignancies; however, based on the studies we reviewed, as well as the related studies for other tumor types, we pose a set of research questions to aid our understanding of these phenomena and lay the groundwork to potentially improve outcomes for patients with these diseases. First, a critical gap in our understanding is the determination of clinically significant delays in referral or diagnosis for chronic hematologic malignancies. Although some studies have described the average amounts of time patients spend in phases of diagnostic work up, referral, and treatment, it is important to understand which delays are specifically associated with adverse outcomes. Here, rigorous and reproducible definitions of delay are essential. Second, determining the impact of delays in differently financed and managed health care systems would help identify which policy initiatives appear to improve timeliness of care and could be considered models for adoption by other countries. For the United States, both of these questions might be answered by utilizing known high-quality data sources such as SEER-Medicare.

Finally, the literature we reviewed contained widely inconsistent approaches to measurement, study design, and data analysis which reduced the ability to make meaningful conclusions. In addition, certain diseases such as CLL and MDS have been completely ignored. Studies that combine data collected on practitioners and diverse patient populations, coupled with data from utilisation claims and tumor registries are sorely needed. Again, attempts should be made to standardise measures (such as socioeconomic status of patients and practitioner credentials) to enable comparisons across settings. Armed with studies that address these knowledge gaps, intervention research to reduce the adverse outcomes of clinically significant delays in affected patient populations would stand the best chance for efficacy.

## Conclusions

Although the overall literature on delays in referral for hematologic malignancies is sparse, we did find significant delays reported for referrals for NHL and MM. Less clear is whether such delays ultimately affect outcomes for hematologic malignancies, and how to possibly ameliorate them. We explored many possible reasons for diagnostic and referral delays for hematologic malignancies by assessing reported sources of such delays for the solid tumors. Lack of PCP exposure to and knowledge of the chronic hematologic malignancies as well as possible biases due to patient characteristics (such as gender, extremes of age, and race-ethnicity) all likely play a role. The solid tumor literature suggests that patients who present with symptoms are more likely to be referred than those who are asymptomatic, and patient delay in seeking care also seems important.

The *To Err is Human* report by the Institute of Medicine specifically identified delays in diagnosis as a contributor to the so-called quality gap in the American health care system [58]. We found scant research into system issues such as lack of available specialists, or incomplete follow-up after a referral has been arranged (the completed 'pass-off'). Indeed, a recent review of literature focusing on follow-up of abnormal screening findings found that most studies detail only patient factors, with a severe lack of data on the systems and practice issues involved in assuring that a patient with suspected malignancy actually gets from a PCP to a specialist in the setting of an intended referral [59]. Problems here might be highly amenable to centralised intervention, with strategies such as internet-based communication, automated clinical information and clinical decision support systems.

Some studies of delay in lymphoma diagnosis hint that, although patients with hematologic malignancies may experience delays in diagnosis and treatment, such delays may not result in compromised outcomes [40,41]. On the other hand, as modern oncologic treatments (e.g. targeted therapy for CML and NHL) and molecular prognostic tools (e.g. fluorescent *in situ* hybridisation for cytogenetic abnormalities in CLL and MDS) come into wider use, earlier intervention may also affect the natural history of disease. In addition, even in the absence of a true survival benefit, there are other favorable outcomes that may result from prompt diagnosis and referral. These possibly include improvements in quality of life, reduced anxiety, access to educational resources and amelioration of complications.

Our review has limitations. First, due to the paucity of articles focusing on hematologic malignancies, it was not feasible to perform a formal meta-analysis or even systematic review with respect to the magnitude of effects seen. Second, many of the studies were descriptive rather than analytical, although this is a result not of our methods but of the quality of the available literature. Third, many of the studies reported were performed in centralised health care systems, which arguably have only modest relevance to the United States, where a large number of patients are uninsured and/or self-referred. Finally, due to its very nature, our type of review is open to the potential bias of selected papers, selected extraction of data from these papers, and the authors' experiences of delay and its possible effects, which is only partially ameliorated by our efforts to include authors with differing areas of clinical expertise (e.g. oncology, hematology and primary care) and from varying disciplines (e.g. nursing, medical and behavioral).

In summary, delays in referral and diagnosis for patients with chronic hematologic malignancies may be significant, may occur along different steps in the pathway towards receiving treatment, and are likely affected by patient and provider characteristics (as well as the interaction between the two). Relatively little information exists on the extent of diagnostic and treatment delays for patients with hematologic malignancies (especially for CLL and MDS). Additional studies to elicit the contributors of delay, the outcomes associated with delay, and interventions to increase PCP awareness and decrease delay are needed.

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