Supporting Clinical Decision Making in Cancer Care Delivery

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Submitted in partial fulfillment of the requirements for
the degree of Doctor of Philosophy
under the Executive Committee of the Graduate School of
Arts and Sciences

COLUMBIA UNIVERSITY

2019
Abstract
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Background

Cancer treatment and management require complicated clinical decision making to provide the highest quality of care for an individual patient. This is facilitated in part with ever-increasing availability of medications and treatments but hindered due to barriers such as access to care, cost of medications, clinician knowledge, and patient preferences or clinical factors. Although guidelines for cancer treatment and many symptoms have been developed to inform clinical practice, implementation of these guidelines into practice is often delayed or does not occur. Informatics-based approaches, such as clinical decision support, may be an effective tool to improve guideline implementation by delivering patient-specific and evidence-based knowledge to the clinician at the point of care to allow shared decision making with a patient and their family. The large amount of data in the electronic health record can be utilized to develop, evaluate, and implement automated approaches; however, the quality of the data must first be examined and evaluated.

Methods

This dissertation addresses gaps the literature about clinical decision making for cancer care delivery. Specifically, following an introduction and review of the literature for relevant topics to this dissertation, the researcher presents three studies. In Study One, the researcher explores the use of clinical decision support in cancer therapeutic decision making by conducting a systematic review of the literature. In Study Two, the researcher conducts a quantitative study
to describe the rate of guideline concordant care provided for prevention of acute chemotherapy-induced nausea and vomiting (CINV) and to identify predictors of receiving guideline concordant care. In Study Three, the researcher conducts a mixed-methods study to evaluate the completeness, concordance, and heterogeneity of clinician documentation of CINV. The final chapter of this dissertation is comprised of key findings of each study, the strengths and limitations, clinical and research implications, and future research.

Results

In Study One, the systematic review, the researcher identified ten studies that prospectively studied clinical decision support systems or tools in a cancer setting to guide therapeutic decision making. There was variability in these studies, including study design, outcomes measured, and results. There was a trend toward benefit, both in process and patient-specific outcomes. Importantly, few studies were integrated into the electronic health record.

In Study Two, of 180 patients age 26 years or less, 36% received guideline concordant care as defined by pediatric or adult guidelines, as appropriate. Factors associated with receiving guideline concordant care included receiving a cisplatin-based regimen, being treated in adult oncology compared to pediatric oncology, and solid tumor diagnosis.

In Study Three, of the 127 patient records reviewed for the documentation of chemotherapy-induced nausea and vomiting, 75% had prescriber assessment documented and 58% had nursing assessment documented. Of those who had documented assessments by both prescriber and nurse, 72% were in agreement of the presence/absence of chemotherapy-induced nausea and vomiting. After mapping the concept through the United Medical Language System and developing a post-coordinated expression to identify chemotherapy-induced nausea and...
vomiting in the text, 85% of prescriber documentation and 100% of nurse documentation could be correctly categorized as present/absent. Further descriptors of the symptoms, such as severity or temporality, however, were infrequently reported.

Conclusion

In summary, this dissertation provides new knowledge about decision making in cancer care delivery. Specifically, in Study One the researcher describes that clinical decision support, one potential implementation strategy to improve guideline concordant care, is understudied or under published but a promising potential intervention. In Study Two, I identified factors that were associated with receipt of guideline concordant care for CINV, and these should be further explored to develop interventions. Finally, in Study Three, I report on the limitations of the data quality of CINV documentation in the electronic health record. Future work should focus on validating these results on a multi-institutional level.
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Acknowledgements

I would like to thank many individuals without whom this dissertation would not have been possible.

First, to my advisor, Dr. Rebecca Schnall, in addition to being brilliant in so many ways, I cannot thank you enough for your support for me to carve out a dissertation in an area I care deeply about, and for simultaneously opening my eyes to the world of information technology and human computer interaction.

I also thank my dissertation committee: Dr. Chunhua Weng, Dr. Dawn Hershman, Dr. Lillian Sung, and Dr. Maura Abbott. I was lucky enough to take Dr. Chunhua Weng’s course, Symbolic Methods, in the Department of Biomedical Informatics, and not only did this impart upon me the importance of terminologies, how they are understood by different disciplines, and the importance of clarity, but I was able to develop my term project into the third study of this dissertation with her continued guidance and mentorship. Dr. Dawn Hershman has provided mentorship both in my role with the Columbia University Minority-Underserved NCI-Community Oncology Research Program and as I develop my program of research in Cancer Care Delivery. Her clear, thoughtful approaches toward changing practice in cancer care is inspiring, and I am grateful for the opportunity to continue working with her in my postdoctoral fellowship. Dr. Lillian Sung has been the most influential clinician and researcher in pediatric oncology to me, and she has helped to change the way we approach supportive care in pediatric cancer, improving the lives of many patients. She gave me my first opportunity to become more involved in research by inviting me to join the Cancer Control Steering Committee and subsequently the Cancer Care Delivery Steering Committee in the Children’s Oncology Group. She has taught me the importance of scientific rigor and to be careful in the way we ask research...
questions, but also the importance of promoting a supportive, welcoming environment with colleagues, for which I am grateful. I thank Dr. Maura Abbott for meeting with me before I applied for the PhD program and for encouraging me to pursue this career path.

I also want to thank Dr. Suzanne Bakken for her support through the Reducing Health Disparities Through Informatics T32 training program, but also for her advice throughout my predoctoral training related to informatics, postdoctoral programs, and career development.

To my cohort, as we all know, it truly takes cohort support. Aluem, Meg, Richard, Hyejin, and Victoria, and to the cohorts ahead and behind us—it really takes a village. That we may all remember the importance of collegial support and carry it through our careers with us, lifting up others when they need it and asking for help when we need it ourselves.

And to Judith Kelson…thank you for helping us all navigate the world of CUSON’s PhD program.

To my pediatric oncology family—the nurses, physicians, social workers, and everyone else who makes this work all the more enjoyable and inspiring. Especially, to Becca, Ann, and Jackie. And to the children, adolescents, and young adults with cancer who have inspired the questions that led to this dissertation and continue to motivate me every day. And of course, to their families: parents, brothers, sisters, relatives, and families: thank you for allowing us into your worlds. I hope we can always continue to improve the care that we provide.

Finally, I want to thank my family. Their support and love are the two reasons why I am here, and I am incredibly grateful. John and Aileen Parsons, for your love and support but also for your emphasis on education and on the importance of pursuing new knowledge; and for your very helpful support spending extra time with Iris and Eve over the past few years, thank you.
Karen and Bob Beauchemin, thank you also for your support. Heather Parsons, for your unwavering support, and for our friendship—sharing the ups and downs throughout our careers and motherhood makes this all the more enjoyable. Ashleigh Parsons, for our long existential talks and walks that often help clarify my research question, and also, for the occasional California visits with included babysitting, I thank you. And finally, to Jeremy, Iris and Eve: I love you. Jeremy, your calm presence really is amazing—I am lucky to call you my best friend. And to Iris, thank you for talking through some of my toughest questions when it was really time for bed, and for your pragmatic responses. And to Eve, thank you for your smiles, laughter, and intense hugs.

**Funding**

The author is currently a predoctoral trainee on the Reducing Health Disparities Through Informatics (RHeaDI) (T32NR007969). RHeaDI is an NIH-funded fellowship program for pre- and post-doctoral fellows with a goal of preparing nurse scientists to conduct interdisciplinary informatics research to advance nursing science and health equity. The author is supported by a Doctoral Degree Scholarship in Cancer Nursing, DSCN-18-068-01, from the American Cancer Society.
Dedication

This dissertation is dedicated to the children, adolescents, and young adults who have inspired me to go into this field since 2000; especially to Mervin and his mom because families belong together.
Chapter One: Introduction

Chapter One outlines the organization and background of this dissertation. It begins by describing cancer care in the United States (US) and then focuses on a specific patient population: children, adolescents, and young adults with cancer. Challenges with treating these patients, specifically related to symptom management are then discussed. A specific symptom, chemotherapy-induced nausea and vomiting is explicitly discussed including the prevalence, impact on patients, and availability of clinical practice guidelines that provide prevention and management strategies. Barriers to guideline implementation are then outlined, both generally, but also specifically related to supportive care guidelines in children, adolescents, and young adults with cancer. Then the background shifts to describe strategies that may improve implementation of guidelines, specifically using informatics-based approaches such as clinical decision support. The increasing use of electronic health records and the importance of integrating decision support as well as patient-reported information into the electronic health record are discussed. The theoretical framework utilized in this research is then described, and finally, the plan for three manuscripts and their respective aims are summarized.

The first manuscript (Chapter Two) is currently under revisions for the International Journal of Medical Informatics. The second manuscript (Chapter Three) is planned for submission to Supportive Care in Cancer. The third manuscript (Chapter Four) is planned for submission to the Journal of American Medical Informatics Association.

Current Complexities in Cancer Treatment

40% of the US population will be diagnosed with cancer during their lifetime, and although the treatment and prognosis depends on the type and stage of cancer, the majority of
cancer patients will undergo intensive treatment either for curative or palliative intent.\textsuperscript{1} Although many cancers have clear treatment guidelines available, decision-making for cancer treatment is complex. First, the era of precision medicine and genomic testing has introduced a treatment landscape often with one or more possible treatment options.\textsuperscript{2} Second, factors such as patient age, clinical or performance status, and a patient’s insurance status may influence the prescribed treatment plan.\textsuperscript{3,4} Finally, our ability to predict, diagnose, and treat both cancer- and therapy-related toxicities has improved greatly, further complicating decision making to individualize each cancer patient’s treatment plan. During treatment, following treatment, or at time of relapse, additional decision-making time points occur, and providers are expected to have the most updated information to inform shared decision making with a patient and their family.

Cancer treatment is also associated with significant side effects. Treatment modalities include chemotherapy, targeted therapiies, radiation therapy, and/or surgery. These treatments are often intensive and associated with significant acute side effects and long-term morbidity, such as nausea, vomiting, fatigue, infection, chronic pain, neuropathy and cardiac complications.\textsuperscript{5-7} These and other side effects of therapy negatively impact a patient’s symptom experience and quality of life.\textsuperscript{7-9} Poorly-controlled symptoms may also cause a delay in curative treatment or non-adherence to the treatment plan, jeopardizing a patient’s survival.\textsuperscript{10,11} Many of these treatment-related symptoms, however, can be palliated, and a substantial body of evidence-based research exists to provide guidance on the best practices for prevention and treatment of many cancer-related symptoms.\textsuperscript{12-17} There is unfortunately a wide variability in clinical settings, and these guidelines are not consistently implemented in practice.\textsuperscript{18,19}

In addition to the challenges of clinically managing an individual cancer care, the burden of cancer continues to increase. With an aging population, although the proportion of new cases
of cancer is stable or decreasing, the overall number of patients continues to increase. In addition, the Affordable Care Act has improved access to care in the US, reducing the uninsured rate by 43% from 2010 to 2015. The US healthcare system, therefore, now has more patients with access to care without an equivalent influx of providers, contributing to an increasing workload for prescribers and other clinicians. The costs of cancer are also significant, with treatment-related expenses accounting for 9% of prescription spending for Americans and another 3% or $11.1 billion spent on supportive care medications to alleviate treatment-related symptoms.

**Pediatric, Adolescent and Young Adult Cancers**

Since the 1970’s, the survival rates for most types of pediatric and adolescent cancers have improved with about 80% of pediatric patients now expected to become long-term survivors (at least 5 years from diagnosis). These successes, however, require intensive and frequent therapy that is often the cause of significant side effects and morbidity. The majority of children with cancer experience bothersome side effects during their treatment, most commonly fatigue, nausea, and pain. Similar to adult data, increased symptoms in younger patients are also associated with poorer psychological outcomes and health-related quality of life. Due to the high cure rates in childhood cancers, however, these symptoms and their potential negative effect on long-term outcomes are sometimes overlooked due to the importance of and likelihood of cure.

For adolescents and young adults with cancer, broadly defined as ages 15 – 39 years of age, the survival outcomes are less optimistic than their younger counterparts with the same types of cancer. In addition to biologic differences in disease, a significant reason for poorer survival for adolescents and young adults is they do not tolerate the pediatric regimens as well as
younger children and experience more side effects and symptom burden.\textsuperscript{30-32} Erickson et al\textsuperscript{32} conducted a review of symptoms in adolescents receiving chemotherapy and found that adolescents experience multiple distressing symptoms during chemotherapy, including fatigue, sleep disturbances, pain, nausea/eating problems, mood disturbances, and appearance changes. A qualitative study of adolescents and young adults identified symptoms, specifically pain, nausea, and vomiting, as a significant concern during cancer treatment.\textsuperscript{33} Although there is a wide age range, the importance of developmental milestones, such as formal cognition, independence, and sense of self may be hindered due to a cancer diagnosis and necessary treatment.\textsuperscript{34} In addition, adolescents and young adults with cancer may experience logistical challenges affecting their ability to adhere to treatment and symptom management recommendations. These include poorer access to care due to transportation challenges, poorer insurance coverage, and less direct support from parents, family, and peers.\textsuperscript{35,36}

**Chemotherapy-induced Nausea and Vomiting**

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common treatment-related symptoms affecting up to 80\% of all cancer patients.\textsuperscript{6,27,37} It is also cited by patients as one of the most feared adverse effects of cancer treatment.\textsuperscript{6,38,39} Chemotherapy is classified by emetogenicity, or its propensity to cause nausea and/or vomiting;\textsuperscript{40-42} most commonly the classes are high (emetic risk >90\%), moderate (30-90\%), low (10-30\%), and minimal (<10\%). In addition to the cause, CINV is classified temporally as acute, delayed, anticipatory, and breakthrough or refractory.\textsuperscript{43} Risk factors in adult cancer patients have been identified and include gender (female > male),\textsuperscript{44} age (< 55 years),\textsuperscript{45} cycle of chemotherapy (initial > subsequent),\textsuperscript{46} prior morning sickness with pregnancy, and alcohol intake.\textsuperscript{47}
In children with cancer, little is known about risk factors outside of the emetogenic potential of the chemotherapeutic agents. A study of children with acute myeloid leukemia found a significant association of antiemetic alteration, a validated proxy measure for the experience of CINV, and increasing age \((P<.001)\). In addition, this study found that the rate of antiemetic rescue, providing an adjunct therapy for treatment of CINV, in privately insured patients compared with publicly insured patients was significantly lower, suggesting a disparity in how CINV is assessed and/or managed.

Although risk factors for CINV in children with cancer are less well understood, studies have found it is a common and persistent cancer-related symptom. A longitudinal study of children with standard-risk acute lymphoblastic leukemia (ALL) assessed common symptoms over time, including procedure- and treatment-related anxiety, pain, and nausea by parental report, and it found that nausea was among the most common symptoms with 47% of patients reporting it at the start of the study. In addition, although most symptoms improved over the course of treatment, the mean score of nausea was significantly worse at both 6- and 12-months after diagnosis compared with 1-month after diagnosis \((P<.0001)\). This is important for three reasons: first, it highlights the persistence of CINV as a symptom and the difficulty in achieving complete control for many patients; second, patients who have poorly controlled nausea with their first chemotherapy administration have an increased likelihood of refractory, breakthrough, and anticipatory nausea; and third, it suggests that screening for nausea may be less frequent in later phases of treatment, and therefore, treatments less frequently prescribed or administered.

In studies of adolescents with cancer, CINV has been reported in 50 – 100% of patients receiving chemotherapy. Less is known about the prevalence and severity of symptoms in young adults; however, a qualitative study to explore issues experienced by young adults during
cancer treatment reported that 84% of participants cited symptoms as the most important factor affecting health-related quality of life.\textsuperscript{33} In addition, it is well-established that adolescent and young adults with cancer have poorer survival outcomes\textsuperscript{51} compared to younger pediatric patients, often attributed to lower rates of health insurance coverage,\textsuperscript{52} lower rates of participation in clinical trials,\textsuperscript{53} and poorer biology of cancer.\textsuperscript{54} Insurance status directly relates to access to care, including supportive care measures, and because treatment adherence can be affected by symptoms like CINV, it is important to optimally manage symptoms as this may help to improve survival.

**Clinical Practice Guidelines**

Although cancer treatment and management are complex, effective strategies to predict, prevent, identify, and manage cancer have been described in the literature. Many of this guidance comes from clinical practice guidelines, defined by the Institute of Medicine in a 2011 report as “statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.”\textsuperscript{55} Guidelines are developed through a rigorous systematic methodology synthesizing the ever-increasing amounts of published literature into a practical and digestible set of clinical recommendations to be used in a healthcare setting.\textsuperscript{56,57} The Grading of Recommendations Assessment, Development and Evaluation (GRADE) collaboration developed a widely-accepted approach for developing guidelines by rating both the quality of the evidence and the strength of the recommendation.\textsuperscript{58} The U.S. Preventive Services Task Force also develops guidelines using a similarly rigorous and transparent methodology.\textsuperscript{59} Both recognize that guidelines need to be trustworthy and understandable, and the goal is to direct clinicians in providing the most up-to-date, evidence-based, and highest quality care for their patients.
Chemotherapy-induced Nausea and Vomiting Guidelines

Poor management of symptoms, specifically CINV, is particularly worrisome because medications are available to effectively prevent or manage it. Robust guidelines have been developed for the prevention and treatment of CINV both for adult and pediatric cancer patients. Provision of guideline concordant care (GCC) improves patient symptoms, as demonstrated in a study where GCC was provided to adult patients. Complete response (i.e. no symptoms of nausea or vomiting) was achieved in a significantly higher number of patients receiving GCC compared with those receiving guideline-inconsistent care (aOR 1.43; CI95 1.04 – 1.97).

For pediatric cancer patients, all available guidelines recommend that children receiving highly- or moderately-emetogenic chemotherapy (HEC or MEC) receive a 5HT3-blocker (e.g. ondansetron, granisetron) and dexamethasone, a corticosteroid, for prevention of CINV. In addition, for patients receiving HEC, an additional class of medications, neurokinase inhibitors (NK1RAs) (e.g. aprepitant, fosaprepitant), are also recommended. The 2013 guideline for pediatric patients restricted this recommendation only to patients greater than age 12 years; however, the updated 2017 guideline for CINV prevention in pediatric cancer patients recommends an NK1RA for anyone receiving HEC older than 6 months of age. In adults, the guideline recommendations are similar, recommending a 5HT3-blocker and dexamethasone to prevent acute CINV in patients receiving MEC, and the addition of an NK1RA for patients receiving HEC.

Disparities in the Delivery of Guideline Concordant Care

There is wide variability in clinical practice, however, and providers do not consistently follow these guidelines. Two studies examining adherence to guideline recommendations for
prevention of CINV in adult cancer patients demonstrated racial and socioeconomic disparities in receipt of GCC. A recent study of breast cancer patients found that 60% of patients did not receive the recommended prophylactic treatment for CINV. They also demonstrated a racial disparity with black women being significantly less likely to receive NK1RAs than white women (aRR=0.68, 95% CI 0.51–0.91; P < .05).66 Another study of newly-diagnosed lung cancer patients found that individuals in the highest income quartile had significantly higher likelihood of receiving National Comprehensive Cancer Network-recommended CINV treatment compared with those in the lowest income quartile (OR=1.622; 95% CI 1.367-1.924; P < .001).67

In pediatric, adolescent and young adults with cancer, studies have shown that administration of an appropriate antiemetic significantly reduces both nausea and vomiting.18,68 These studies, however, described the efficacy of antiemetic treatment in controlled clinical trials and did not examine the proportion of patients receiving GCC in a real world setting. Little is known about the predictors of children, adolescents and young adults receiving GCC. This is important to understand given that there are effective treatments for CINV, and not adhering to the guidelines may worsen patient symptoms, increase risk of dehydration, decrease patient-reported quality of life, and worsen adherence with prescribed treatment regimen.49,69,70

**Challenges in Guideline Implementation**

Although our literature is replete with guidelines, the expected improvements in patient outcomes and reduction in healthcare-related costs have not followed.56,71,72 Studies have demonstrated that on average, it takes 17 years for 14% of knowledge to be translated into clinical practice,73,74 and in response to this, research has broadened to focus on how guidelines can be effectively implemented in a clinical or community setting.75,76 The transdisciplinary field of implementation science has been established, and the complexities of translating
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evidence into practice are numerous. For example, the Expert Recommendations for Implementing Change (ERIC) project\textsuperscript{76} named 73 implementation strategies, highlighting the extensiveness and complexity of implementation studies. These strategies aim to enhance the adoption, implementation, and sustainability of a clinical program or practice\textsuperscript{77,78}. This area of research requires an ongoing, iterative and constant feedback mechanism. These studies, therefore, include outcomes that differ from traditional research outcomes such as efficacy or effectiveness, and instead highlight the acceptability, appropriateness, costs, and sustainability of the implementation strategy\textsuperscript{79,80}.

Because of the time lag identified in implementing research into practice, research on the barriers to implementation have also been published\textsuperscript{71,81}. Barriers are similarly complex and may vary by the implementation strategy being utilized, setting characteristics, provider and cultural characteristics, and the evidence or practice change that is being implemented. Factors associated with guideline adherence include provider-level, system or hospital-level, patient-level characteristics as well as provider-patient communication\textsuperscript{82,83}. The greatest likelihood of implementation of guidelines into clinical settings is seen through multi-level approaches that integrate outcomes such as acceptance into practice, sustainability, and even deimplementation of practices that are determined to no longer be effective or appropriate\textsuperscript{84}.

**Clinical Decision Making**

Clinical decision making is a complex process and requires clinicians to harness large amounts of patient-generated and evidence-based data to provide the best care\textsuperscript{85,86}. This is challenging, however, and studies have shown that clinicians may over- or underestimate the risks and benefits of available treatment\textsuperscript{87}. In addition to synthesizing the available evidence, clinicians should make treatment decisions with consideration of patient preferences. This shift
toward patient-centered care ideally leads to shared decision making, a model of care that may help to improve care and reduce healthcare costs.\textsuperscript{88} Shared decision making involves the patient, often family members, and clinician(s) working as a team to make the most appropriate decision for an individual patient. This model is especially useful when more than one option for care exists. One can argue that this is found in most healthcare settings, as continued advances in medicine and precision health allow for multiple and tailored treatment options.\textsuperscript{89,90}

The availability of more than one treatment option, however, leads to increasingly complicated decision making in a healthcare system where it is challenging to have enough time and resources to make the best decision for each individual patient while incorporating cultural, religious, and other personal considerations.\textsuperscript{91} It is important to identify strategies that can harness these data and considerations in support of clinicians to provide cancer patients the highest quality of treatment and supportive care. Previous research has shown that computerized clinical decision support systems have the potential to successfully support this goal.\textsuperscript{92,93}

\textbf{Clinical Decision Support}

Clinical decision support (CDS) should “provide clinicians, staff, patients, or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care.”\textsuperscript{94} The premise for CDS is not that the technology should replace the clinician and make the decision, but that, due to the huge amount of information available in healthcare settings, the technology can serve as a guide or support to help the clinician to make the right decision for the right patient at the right time.\textsuperscript{86} Three concepts, or pillars, are required to give CDS the best chance of success in a clinical setting: evidence and knowledge base, clinician adoption, and consistently-updated information.\textsuperscript{94}
First, the highest quality of evidence, or knowledge, must be available at the time when it is most needed. This requires a computable representation, or a clear organization of the information that is readily searchable and interpretable for the relevant clinicians or users of the information. The information that the computable representation is built on should be based off the most updated evidence, and in cancer treatment and supportive care decision making, there is a large volume of literature to support this.\textsuperscript{65,95-98}

Second, CDS must have a high adoption rate and be effective in the delivery of the information. This requires a clear and well-developed implementation strategy from CDS development to clinician and point-of-care delivery. This pillar will need input from the healthcare provider as the end-user of a CDS system to ensure the system is usable and acceptable. Building a CDS system, therefore, will require adequate stages of usability testing to ensure its success.\textsuperscript{85,99}

Finally, CDS must undergo consistent updates and improvement to ensure not only that the knowledge informing the CDS is updated but also that the strategy for implementing the CDS is also evaluated and updated. This step initially requires an intensive process of manual review and updates of the available literature and evidence; however, a feedback system that continually learns from itself is possible and can result in an automated updating procedure.\textsuperscript{100,101}

A recent National Academy of Medicine meeting on CDS discussed its challenges and strategies to harness its potential in an increasingly-automated and technically-capable healthcare system.\textsuperscript{102} Focus should be on creating standards and incentives to use CDS, improving the evaluation of CDS, identification of clear measures of success, increasing engagement of stakeholders, specifically clinicians, in the design, implementation, and usability of CDS, and incorporating new knowledge, specifically patient-generated and patient-reported data into CDS
through integration and interoperability of electronic health record (EHR) systems. These statements highlight the importance and capability that CDS should continue to have in our healthcare system.

**Electronic Health Record Data: Benefits and Challenges**

Changes to the US healthcare system, specifically the Affordable Care Act in 2008 and subsequently, Meaningful Use in 2010, increased the adoption of EHRs. As of 2016, 95% of hospitals eligible for the Medicare and Medicaid EHR Incentive Program were using health information technology to meet the required standards. This has led to an increasing capacity to improve the EHR infrastructure, streamline clinical information, and ultimately lead to improvements in healthcare through safer, higher-quality, and more efficient care.

As we move toward an era of rapid learning health systems in oncology care, the historical silos of single-institution data collection, storage, and management become increasingly important to exploit and adapt into an interoperable, transparent approach toward data collection methods. This system, as described by the American Society of Clinical Oncology, requires information-rich, patient-focused data, that can then be aggregated and synthesized into new evidence that will drive and transform cancer care delivery simultaneous to rigorous evaluation of patient-provider- and system-level outcomes. This iterative process necessitates ongoing forward movement and integration as new technology and methods become available.

An integral component of this interoperability, implementation of the EHR, however, has been complex, and new challenges to care delivery have emerged. Meaningful Use acknowledges the need for calibrating the speed of EHR-adoption to the capacity of the end-users, healthcare providers. Limitations remain, however, with EHR data not meeting newly-
developed data quality standards specifically relating to completeness, concordance, and plausibility.\textsuperscript{105} The limitations of EHR data inform a growing body of literature, and frameworks and desiderata have been developed to guide the requirements for high-quality, accurate EHR data, mostly based on common data element requirements.\textsuperscript{105,106} The goal of these standards is to achieve an EHR with patient information that are usable and optimized for interoperability.

**Patient Reported Outcome Measures**

A major limitation of EHR data relates to incompleteness, discordance, and heterogeneity of the data. Because historically, EHR data was developed for billing purposes, the current EHR systems have limited capabilities related to patient outcomes. Numerous patient-reported outcome measures (PROMs) have been developed and validated across patient populations,\textsuperscript{107,108} and these measures are acceptable to patients and feasible to collect. Importantly, routine screening of PROMs has been linked to improved symptoms, perhaps by bringing patient awareness and encouraging symptom self-management. Routine symptom screening using PROMs has in fact been linked to an improvement in survival in cancer patients.\textsuperscript{109,110} These measures, however, are primarily used in clinical research settings and may not be integrated into EHR systems. Barriers to implementation of PROMs include the variability of measures across institutions, time constraints, difficulty interpreting PROMs results, and liability concerns.\textsuperscript{111,112} Facilitators to the use of PROMs in clinical settings have also been described, and integration of the PROMs with clinical practice guidelines to deliver a clinical decision support may be an enabler.\textsuperscript{113} EHR-integration of PROMs have been developed and tested,\textsuperscript{114} but are not routinely and consistently implemented nor are findings disseminated in the US healthcare system. PROMs can both improve patient symptom management but can also support the completeness,
concordance, and reduce heterogeneity in EHR data. Therefore, EHR-integration should be studied and developed further.\textsuperscript{115}

**Importance of Standardized Data Elements**

The Observational Medical Outcomes Partnership (OMOP) has developed a Common Data Model (CDM) to transform data from multiple settings into a common format as well as map EHR data to standardized terminology.\textsuperscript{116} The OMOP-CDM is one example of a CDM that can support big-data healthcare analyses. Standardized terminologies have been developed in many domains of healthcare, and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) and Systematized Nomenclature of Medicine - Clinical Terms (SNOMED-CT)\textsuperscript{117} are clinical terminologies used by health care providers for the electronic exchange of clinical health information. In addition to standardized terminologies, the Unified Medical Language System (UMLS)\textsuperscript{118} is a compendium of multiple vocabularies that utilizes the OMOP CDM in an effort to improve clinical data sharing and support interoperability.\textsuperscript{119}

With the concurrent increase in EHR use in the U.S. healthcare system, research has shifted to understand how standardized terminologies and informatics can drive new research. First, a system that follows the recommendations outlined by the data quality standards will be able to better utilize the clinical data to inform CDS systems and increase clinician awareness of and adherence to evidence-based guidelines.\textsuperscript{120,121} CDS requires a computable representation of the clinical data, and its success is largely dependent on unambiguous, complete, and correct documentation or data feeding the CDS system.\textsuperscript{94}

Second, because of the vast amount of information in the EHR, there is considerable effort being expended to optimize these data to support further knowledge generation and
research initiatives through secondary use of the data.\textsuperscript{105} Data quality standards should be used to guide the structure of a clinical data warehouse to better support retrospective research studies. By curating the data in a standardized way with common data elements, these data can be harnessed to assess existing evidence and determine if the findings are reproducible, adding rigor to our current evidence.\textsuperscript{122} With standardized documentation guidelines, machine-readable algorithms can then reliably use the standardized EHR data to develop phenotypes and subsequent cohort studies.\textsuperscript{106} This methodology has been used in multiple settings; however, cancer-related symptom cohorts have not been studied.\textsuperscript{123}

\textbf{Knowledge to Action: Conceptual framework}

The Knowledge to Action (KTA) framework\textsuperscript{124} is the guiding framework for this dissertation (Figure 1.1). Knowledge translation, the key concept within this framework is one of many terms used in the field of implementation science and was defined in 2006 as “a dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically sound application of knowledge to improve health, provide more effective health services and products and strengthen the healthcare system.”\textsuperscript{125,126} The related framework that was published in 2011 describes two distinct components of knowledge translation: knowledge creation and the action cycle, or application of the knowledge. This dissertation focuses both on the action cycle and the funnel of knowledge creation, acknowledging the fluidity of these two domains and the interrelatedness between them (Figure 1.2). Although this dissertation does not propose to develop new clinical practice guidelines, each of the distinct studies identifies new areas of knowledge that inform the iteration of our action cycle and will provide a framework to evaluate outcomes in future studies.
The KTA framework is well-established in the fields of Implementation Science and Decision Making and so it is particularly well-suited to the proposed work. This dissertation focuses on the identification of previously-established knowledge (evidence-based clinical practice guidelines), how this evidence can be implemented into clinical care (clinical decision support), the processes for translating this into clinical care (rate of guideline concordant care), and documentation within the electronic health record (completeness, concordance, and heterogeneity).

Figure 1.1: Knowledge to Action Process Framework
Figure 1.2: Conceptual framework. Adapted from Graham (2006)
Specific Aims

This dissertation aims to address three gaps in clinical decision making in cancer care delivery. Specifically, the aims are to:

**Aim 1:** Conduct a systematic review to identify clinical decision support (CDS) systems that have been used to assist in decision making for the therapeutic management of cancer

   **Aim 1a:** Determine the impact of the CDS on process- and patient-specific outcomes

**Aim 2:** Determine the rate of guideline concordant care for the prevention of CINV in children, adolescents, and young adults with cancer receiving emetogenic chemotherapy

   **Aim 2a:** Identify predictors of guideline-consistent care for the prevention of CINV in children, adolescents, and young adults with cancer receiving emetogenic chemotherapy

**Aim 3:** Examine the documentation of CINV in the EHR to describe the completeness, concordance, and heterogeneity of electronic health record documentation regarding chemotherapy-induced nausea and vomiting

   **Aim 3b:** Map the concept of CINV through UMLS to develop post-coordination expression and determine gaps in the concept definition to strengthen the data capture processes with SNOMED-CT crosswalk through UMLS
Chapter Two: Clinical decision support for therapeutic decision-making in cancer: A systematic review

The study in Chapter Two addresses the first aim of the dissertation in a systematic review to identify clinical decision support (CDS) systems that have been used to assist in decision making for the therapeutic management of cancer, and to determine the process and patient-specific outcomes.

Abstract

Cancer management, including supportive care, is complex and requires availability and synthesis of published and patient-specific data to make appropriate therapeutic decisions. Clinical decision support (CDS) may be an effective implementation strategy to support complex decision making although it is unclear whether it improves provider outcomes, patient outcomes or both in cancer settings. We therefore conducted a systematic review to identify CDS that have been used to support therapeutic decision making in clinical cancer settings. Outcomes of interest included process outcomes or the effect of CDS on the clinician’s decision making, and the patient’s clinical response. Ten studies met inclusion criteria, with variability in the study design, setting, and intervention. Of the nine studies that measured process outcomes, four demonstrated significant improvement; and of the six studies that measured patient outcomes, four demonstrated significant improvement. All included studies utilized CDS that were informed by clinical practice guidelines while only three were integrated into the electronic health record. In conclusion, CDS to guide cancer therapeutic decision making is an understudied but promising area. Further research is needed.
Background

Forty percent of the US population will be diagnosed with cancer during their lifetime, and although the treatment and prognosis depends on the type and stage of cancer, the majority of cancer patients will undergo intensive treatment either for curative or palliative intent.1 Further, provision of supportive care is important to maximize quality of life during treatment and to minimize late effects of therapy. Although treatment guidelines have been developed for many cancers, decision making for cancer management is complicated because many factors influence the best treatment plan for an individual patient. First, the era of genomic testing and precision medicine has introduced a more complex treatment landscape due to the heterogeneity of cancer as a disease and provided insight into individual susceptibility to toxicities and late effects.2 Second, factors such as patient age, patient functional or clinical status, patient or provider preferences and values or patient insurance status may influence the prescribed treatment plan.3,4 Finally, our ability to predict, diagnose, and treat both cancer- and therapy-related toxicities has improved greatly, and this sometimes allows for multiple options for an individual’s treatment plan. For each clinical decision, providers are expected to have the most updated information to inform shared decision making with a patient and their family.127,128

In addition to the complexities of clinically managing cancer, the burden of cancer continues to increase, primarily due to an aging population.20 The increasing burden of cancer and its costs impact upon clinical demands and overall care delivery.21 Health information technology (HIT) has frequently been cited as a main driver to any proposed solution. HIT is a key contributor to harnessing “big data” and allowing the healthcare system to learn from every patient, better predict the best treatment options and ultimately, deliver high quality care.129 With exponentially-increasing volumes of data becoming available through electronic health records
CLINICAL DECISION MAKING IN CANCER CARE

(EHR) and technology available to process and translate these data into usable predictive algorithms, a rapid learning health system for cancer care seems more tangible than ever.\textsuperscript{130}

Clinical decision support (CDS) is a HIT tool that processes patient-specific information through a previously-determined algorithm and provides clinicians with a data-driven recommendation to support clinician decision making at the point of care.\textsuperscript{102} Three concepts, or pillars, are required to give CDS the best chance of success in a clinical setting: a strong evidence and knowledge base, clinician adoption, and consistently-updated information.\textsuperscript{94} CDS tools or systems were first developed prior to the widespread use of technology in healthcare, and were usually paper-based and knowledge-driven rather than data driven. Although some early CDS systems demonstrated improvement in care delivery, commonly-cited barriers to CDS implementation included poor integration into clinical workflows and inability to constantly update the knowledge base in the CDS tool.\textsuperscript{131-133} Electronic and automated CDS were subsequently developed to overcome these barriers, and implementation of CDS has greater success if it is interoperable and integrated with the EHR.\textsuperscript{134} With suboptimal or lack of interoperability with the EHR, a CDS may not be perceived as useful and accepted into a busy clinical workflow. Ever-increasing HIT capabilities, however, allows novel approaches to address these barriers, and CDS is now considered a highly-valued component of improving care delivery across the healthcare system.\textsuperscript{102,135} Specifically in cancer, CDS has showed promise in cancer screening, prevention, diagnostic, and surgical or radiation oncology settings.\textsuperscript{136-141}

The benefits of CDS in settings where cancer is clinically managed, specifically to provide decision support for disease-directed therapy or supportive care management, however, are not well known. It is unclear whether CDS in these settings improves process outcomes, such as provider adherence to CDS recommendations, patient outcomes, such as reduction of
symptoms or satisfaction with care, or both. Cancer-specific CDS in therapeutic settings should process the current evidence and provide relevant patient-specific knowledge and decision support in an understandable and usable format at the point of clinical care. If integrated into a healthcare setting effectively, CDS may help to support appropriate, evidence-based care and ultimately improve patient outcomes in cancer management. The purpose of this systematic review is to: 1) describe clinical decision support systems that have been used in clinical cancer settings to guide therapeutic decision making, including supportive care management, and 2) measure the effect of CDS on care delivery process and patient outcomes.

Methods

Search strategy

Four databases, PubMed, EmBase, OVID Medline and Institute of Electrical and Electronics Engineers (IEEE) Xplore, were searched to identify studies where electronic or automated CDS was tested to guide cancer therapeutic decision making, including supportive care management (see Appendix 1 for search strategy). The search strategy was developed in consultation with an informationist at the primary author’s academic institution following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study was registered in Prospero (https://www.crd.york.ac.uk/PROSPERO/#recordDetails) and the eligibility criteria for included publications was defined a priori. Our search included studies from database inception through November 2018; we also conducted an updated search in April 2019 to identify any recent publications. For this study, we defined CDS broadly, and searched for terms including: CDS system, decision support system, decision aids and expert systems in our search terms. These terms were based off of prior publications. Inclusion criteria were 1) an electronic-based CDS; 2) studied prospectively in an oncology setting after
the diagnosis of cancer had already been made; 3) delivered CDS to a clinician; 4) the CDS provided therapeutic recommendations; 5) original research study; and 6) full text article was available. Pilot studies were included as long the outcome, effect on care delivery process and/or patients, was reported. Studies were included regardless of publication date or language of publication. We excluded studies using a CDS to support cancer screening, cancer risk-assessment, or cancer diagnosis as these clinical settings often differ from settings where cancer is treated, and symptoms are managed. Similarly, we excluded studies where CDS guided surgical decision making, as this differs from therapeutic decision making. We excluded studies that were conducted retrospectively or post-hoc analyses of primary data. We also excluded studies that only involved the patient and not clinician as this does not fit our a priori definition of clinical decision support but rather falls into symptom screening. Reference lists in the full-text reviewed articles were examined, and relevant articles were included for review.

**Screening, Abstraction, Appraisal and Analysis:**

All eligible studies were entered into an EndNote database and then de-duplicated using the Bramer Method. All citations were then independently screened by two reviewers (MB, MM) by title and abstract using Covidence; reason for exclusion was documented. Any potentially relevant citations were then included in the full text review and the same procedures were repeated. Discrepancies were reviewed, and final consensus was achieved with a third reviewer (RS), when necessary.

After full text review, variables of interest for the data synthesis were extracted from each included article by two reviewers (MB and MM). These included: 1) disease(s) or symptom(s) being treated, 2) geographic location of study, 3) the proportion of clinicians who adhered to the CDS recommendation, 4) patient disease or symptom outcomes, 5) if the CDS recommendation
was based on a clinical practice guideline (CPG), 6) if the CDS was linked or integrated into the EHR. The Joanna Briggs Institute Critical Appraisal Checklist for Quasi-experimental Studies was used to determine the study quality of the included articles. Studies received 1 point for every component met, and total score indicated study quality with 1 – 3 low, 4 – 6 moderate, and 7 – 9 high. Two reviewers (MB and MM) completed the checklist for each of the included studies, and any discrepancies were reviewed for consensus with a third reviewer (RS), when necessary.

All studies were described qualitatively. The CDS were described by study type, geographic location, disease or symptom studied, CDS characteristics. The outcomes of interest were described and synthesized by effect on clinician and/or patient.

Results

Search Results

Our initial literature search retrieved 951 citations; after de-duplication, 663 studies were included for title and abstract screening. Reasons for excluding 565 are listed in Figure 2.1; most studies were excluded either because they described the technical CDS development process or they were clinical practice guidelines and not CDS studies. Ninety-eight studies were included in the full-text review, two of which were identified by reference searching, and ten unique, original studies met our inclusion criteria and were included in the final review.
Figure 2.1: *PRISMA Flowchart for Literature Search*

Table 2.1 summarizes the characteristics and findings in each of the ten included studies. Five were prospective, pre-post designs comparing the effect of the CDS intervention to a prior period without the intervention. Four were single-arm interventional studies, one with multiple time points,148 two utilizing historical controls as a comparison group,149,150 and one without a
comparison group. Only one study was a randomized control trial (RCT). Three studies were conducted in the United States (US), and the remaining seven were conducted in Europe.

Of the ten included studies, three provided decision support for cancer-directed treatment, specifically breast cancer, and the other seven for supportive care or symptom management. Of the latter seven, the most common symptom was cancer-related pain (n=3). Notably, two of these seven studies approached cancer-related symptoms broadly, assessing and providing decision support on multiple symptoms while one study focused on patient distress.

The CDS interventions themselves varied. Three of the studies utilized the same CDS, OncoDoc, however, each study described a different study design or a different setting. The seven studies where the CDS was symptom-focused utilized distinct CDS systems. Six of these interventions utilized patient-reported symptom information that fed the CDS algorithm to prompt and guide a clinician response. The type of CDS systems ranged from passive to active systems. The most passive systems included three studies utilizing the OncoDoc system and Van Erps’ study using the RESPOND system to manage chemotherapy-induced anemia required manual entry of patient characteristics into the system that would then provide a recommendation. Four studies were intermediate in their automated responses, requiring patient-reported information that was processed into the system algorithm and then prompted the provider with a recommendation. Finally, two studies by Bertsche and Christ integrated EHR data into the algorithm that prompted a provider-facing decision recommendation. Three of the ten included studies had CDS interventions integrated into the EHR; one of these studies disclosed the EHR vendor as Epic Systems Corporation. All included studies reported that the CDS provided recommendations from a published clinical practice guideline.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>JBI Quality Score</th>
<th>Study Purpose</th>
<th>Disease or symptom</th>
<th>Study design</th>
<th>No. of sites/providers/patients</th>
<th>CDS informed from guideline</th>
<th>EHR-integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertsche (2009)</td>
<td>8</td>
<td>To test the impact of a CDSS on prescriber deviations from CDS recommendation for CPG-based pain management in cancer patients</td>
<td>Pain</td>
<td>Pre-post interventional</td>
<td>1/NA/100</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bouaud (2001)</td>
<td>4</td>
<td>To test the adherence of physician's treatment decision compared to that provided by a CDSS in breast cancer patients</td>
<td>Breast cancer</td>
<td>Single-arm pilot</td>
<td>1/13/127</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bouaud (2002)</td>
<td>3</td>
<td>To test the adherence of physician's treatment decision (2nd site studied) compared to that provided by a CDSS in breast cancer patients</td>
<td>Breast cancer</td>
<td>Single-arm pilot</td>
<td>1/NR/NR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Christ (2018)</td>
<td>7</td>
<td>To test the impact of a CDSS on pharmacist deviations from CDS recommendation for CPG-based pain management in cancer patients</td>
<td>Pain</td>
<td>Pre-post interventional</td>
<td>2/14/88</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Author</td>
<td>Study Year</td>
<td>Study ID</td>
<td>Objective</td>
<td>Outcome</td>
<td>Intervention/Method</td>
<td>Study Design</td>
<td>Main Findings</td>
</tr>
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<td>----------------------------------------------------------------------------</td>
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<tr>
<td>Cooley (2015)</td>
<td>7</td>
<td></td>
<td>To test the feasibility of symptom screening linked to CDSS for clinicians to manage symptoms</td>
<td></td>
<td>Symptoms (multiple)</td>
<td>Single-arm pilot</td>
<td>1/14/88</td>
</tr>
<tr>
<td>Li (2016)</td>
<td>8</td>
<td></td>
<td>To test the implementation of the Distress Assessment and Response Tool (DART)</td>
<td></td>
<td>Emotional distress</td>
<td>Pre-post interventional</td>
<td>1/16/196</td>
</tr>
<tr>
<td>Mooney (2017)</td>
<td>8</td>
<td></td>
<td>To test the effect of routine symptom screening linked to CPG-based CDS for clinician follow-up on the patient's symptom severity</td>
<td></td>
<td>Symptoms (multiple)</td>
<td>RCT</td>
<td>6/NR/358</td>
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<tr>
<td>Raj (2017)</td>
<td>9</td>
<td></td>
<td>To test the impact of a CDS for prescribers on patient-reported pain intensity levels and opioid prescribing practices in cancer patients</td>
<td></td>
<td>Pain</td>
<td>Pre-post interventional</td>
<td>1/NR/247</td>
</tr>
<tr>
<td>Seroussi (2001)</td>
<td>8</td>
<td></td>
<td>To test the impact of a CDSS for breast oncologists when determining treatment plan for cancer patients</td>
<td></td>
<td>Breast cancer</td>
<td>Single-arm pilot</td>
<td>2/12/70</td>
</tr>
<tr>
<td>Van Erps (2010)</td>
<td>6</td>
<td></td>
<td>To test the impact of an anemia-management CDSS on clinicians' management of cancer patients with anemia</td>
<td></td>
<td>Anemia</td>
<td>Pre-post interventional</td>
<td>1/NR/68</td>
</tr>
</tbody>
</table>
Outcomes

Process outcomes.

There was variability in the outcomes of the ten included studies (Table 2.2). Although all of these studies included the clinician in the intervention as an inclusion requirement, one study did not measure process outcomes or an effect on the clinician’s behavior. Of nine studies that included process outcomes, five studies demonstrated an improvement in the clinician adhering to the CDS recommendation, four of which were statistically-significant (all with p<.001). Two studies did not show a significant difference, and the remaining two studies only provided an estimate of provider adherence. The effect varied and due to different process outcome measures, such as adherence to the recommendation (yes/no), provider intervention based on the CDS (yes/no), or deviation from CPG (multiple measures reported), summarizing the magnitude of benefit would not be appropriate. Table 1 provides further details about the individual process outcomes and effects.

Patient Specific Outcomes.

Patient outcomes were measured in six of the ten included studies. One study assessed mean hemoglobin levels and the remaining five studies assessed patient-reported symptoms, or patient satisfaction (pain n=3, multiple symptoms n=1, distress assessment satisfaction n=1). Four of these six demonstrated an improvement in symptoms or in satisfaction with their care for the patients treated by CDS-informed providers (provided between-group differences with p<.05), and the other two showed no difference in groups. In the studies that showed improvement or benefit to the patient, the outcome measures varied, including pain scores, measured using different instruments, patient satisfaction scores, treatment impact scores,
and mean hemoglobin levels. A more in-depth summary of patient-specific benefit cannot be accurately described because of variability in outcome measures and definitions. Table 1 provides further details about the patient outcomes and effects. None of the studies reported a worsening of symptoms or adverse effect related to the CDS.

**Comparison by Outcome.**

Studies that measured both process outcomes and patient-specific outcome measures (n=5) varied in the agreement of the outcome effects. Three of these studies reported significant improvements in both process and patient outcomes, and all three CDS focused on symptom management: anemia, emotional distress, and pain.\textsuperscript{154,155,158} In addition, two studies, Bertsche et al and Li et al, were integrated into the EHR.\textsuperscript{154,155}
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Process outcome</th>
<th>Statistically significant benefit of intervention on process outcome?</th>
<th>Patient outcome</th>
<th>Patient-reported?</th>
<th>Statistically significant benefit of intervention on patient outcome?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertsche, 2009</td>
<td>Decreased number of patients with at least 1 CPG deviation from 84% to 14% (p&lt;0.001)</td>
<td>Yes</td>
<td>Pain at rest by NVAS in intervention group decreased from 3.0 to 1.5 compared to discharge (p&lt;.01) and during activity decreased from 7.0 to 2.5 (p&lt;.001) in intervention group</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bouaud (2001)</td>
<td>Overall compliance with CDSS recommendation: 61.42% vs 85.03% (p &lt; 0.001)</td>
<td>Yes</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Bouaud (2002)</td>
<td>Overall compliance with CDSS recommendation: 55%</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Christ (2018)</td>
<td>NCCN-CPG adherent pain regimen prescribed not changed (40% vs. 46.9% p=0.97)</td>
<td>No</td>
<td>Patient-reported attainment of analgesia at 24h: 10.5% improvement (33.3% vs 43.8%, p=.78)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reference</td>
<td>Study</td>
<td>Adherence to CDS Recommendation</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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</tr>
<tr>
<td>Cooley (2015)</td>
<td>Adherence of provider to CDS recommendation averaged 57% (95% CI: 52 - 62%)</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Li (2016)</td>
<td>Intervention for depression increased from 7% to 33% (p &lt;.001)</td>
<td>Yes</td>
<td>Patients with intervention reported significantly greater satisfaction with emotional support (no further results available); patients with low income reported greater satisfaction with emotional support (8.67 v 5.75, p &lt; .001) and treatment support (9.23 v 7.68, p &lt; .05)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mooney (2017)</td>
<td>N/A</td>
<td>N/A</td>
<td>Mean treatment impact for intervention group was 3.59 severity points (p &lt; 0.001), 43% of the non-intervention group value. Intervention group had 3x fewer severe days (p &lt; .001) than usual care. 10 of 11 measured symptoms were significantly lower for intervention group (p &lt; .001).</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Authors</td>
<td>Study Details</td>
<td>Intervention</td>
<td>Pre- vs. Post- Intervention</td>
<td>Statistically Significant?</td>
<td>Effect Size</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>--------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Raj (2017)</td>
<td>Proportion of patients starting a new opioid medication was not statistically different between groups (8.8% vs. 10.5%, p=0.69)</td>
<td>No</td>
<td>Mean pain intensity score were 3.6 and 3.3 between pre- and post-intervention groups (between group difference = 0.12, 95% CI: -0.33 - 0.58)</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Seroussi (2001)</td>
<td>Site 1: Adherence 96.6%, compliance 64.28%; Site 2: Adherence 79%, Compliance 88%. (From Escher: increased compliance rate of decisions from 79% to 93%)</td>
<td>Yes</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Van Erps (2010)</td>
<td>Improvement in mean congruence scores to CPG between pre- and post-cohort (3.00 +/- 1.48 compared to 8.18 +/- 1.38, p&lt;0.001)</td>
<td>Yes</td>
<td>Mean hemoglobin levels significantly increased in post cohort (0.80 +/- 1.51 compared to 1.90 +/- 1.61, p&lt;.01) and patients in post cohort more likely to have Hb&gt;=11g/dL (OR3.64 (1.12-11.80, p=0.03))</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Appraisal

Table 2.1 presents the quality score of the studies that were included in this review using the Joanna Briggs Institute quality appraisal tool. Overall, the study quality was determined to be moderate to high with a mean score of 6.8 out of 9. Most studies explicitly asked a research question, defined a comparison or control group, and stated the study period for each group. In addition, attrition was low. Studies published prior to 2009 scored lower than more recent publications.

Discussion

This systematic review of the literature provides a comprehensive summary of the existing studies that have been conducted utilizing CDS to guide therapeutic decision making in cancer settings. We identified ten studies that suggest a trend toward both provider- and patient-benefit. The small number of studies and variable outcome measures, however, are suggestive that this is an understudied area and the effect from CDS interventions on patient outcomes is unclear. Of the nine studies that measured process outcomes, five demonstrated an improvement; and of the six studies that measured patient-specific outcomes, four demonstrated improvement. The findings are discussed here in further detail.

First, because only ten studies met our inclusion criteria, it appears that although there has been much emphasis on utilizing CDS to guide decision making in cancer, these systems have not yet been developed, tested, or published. Our initial literature search identified many studies where CDS systems or tools were under development, with many technical aspects described in detail. Therefore, it may be that these studies have not yet been developed into full, testable CDS or that other barriers have developed. Conversely, it is also possible that CDS have
been developed and are being utilized to guide therapeutic decision making in cancer, but they have not been studied or published. For example, a 2013 ASCO abstract reported on the development of a CancerLinQ CDS that would provide treatment decision support for breast cancer through an algorithm that made the ASCO guidelines machine readable and patient-tailored through CancerLinQ, a rapid learning system for oncology.\textsuperscript{160} This suggests that therapeutic CDS have been developed and are potentially in use but not yet published.

However, it is also possible that CDS relevant for certain diseases and symptoms have not yet been developed at all. This may be due to two possible reasons. First, the heterogeneity of cancer and cancer symptoms may threaten the validity and reliability of a CDS even within a certain cancer setting. For example, the OncoDoc studies encountered many challenges incorporating the complexity of breast cancer treatment into its algorithm and required multiple iterative updates to the algorithm. In addition, common barriers to technology-based approaches, such as cost, usability, and integration into workflow are well-established and may contribute to the lack of full CDS development in this area.\textsuperscript{102}

Another reason for the small number of studies that were identified may be related to the definition of CDS. We defined CDS as an electronic or automated tool or system that processes current evidence in the context of patient-specific information to provide knowledge and decision support to the clinician at the point of clinical care. We only included studies that provided decision support directly to a clinician and was then anticipated to be delivered to the patient.

Our results differ from a recent systematic review of CDS systems in oncology practice.\textsuperscript{161} This review focused on CDS systems used to diagnose, treat, and manage cancer and identified 24 studies. In contrast, our review excluded the diagnostic period which accounts for
some differences in the identified studies. A major difference, however, relates to variability in
definition of CDS. Our search strategies differed slightly, including our inclusion of the terms
“expert system” and “decision aid.”\textsuperscript{94,102,143} We did not include terms “clinical pathways” or
“online order entry” which may account for differences. Finally, we defined clinical decision
support as a system or tool that provides patient-specific information and a recommendation for
management to the provider. We excluded studies where patient-reported symptoms were
captured and informed a prompt for follow-up by a clinician if it did not describe the decision
recommended to the provider.

There has recently been focus on automated patient-reported symptom screening linked
to automated feedback directly to the patient. For example, Basch et al. have extensively studied
a symptom tracking and reporting system that can link to automated feedback compared with
nursing feedback through an email notification.\textsuperscript{162} Although these studies are promising from a
symptom self-management approach, they do not meet our definition of CDS as the nursing
feedback model did not provide decision support to guide the nursing-patient interaction.
Importantly, however, this approach has demonstrated a significant improvement in overall
survival for patients in the intervention arm, meaning that systematic screening of patient-
reported symptoms is associated with better patient outcomes.\textsuperscript{163} An earlier study by Sikorskii et
al compared two multi-modal interventions for symptom management and found that both an
automated intervention and a nurse-assisted intervention significantly reduced patient-reported
symptoms (p < .01).\textsuperscript{164} Again, this intervention did not guide the decision making for the nurse.
Therefore, in these and other similar studies\textsuperscript{165} it is unclear how or if high-quality feedback, such
as guideline-informed care, is being provided to the clinician. Novel approaches to this
challenge, such as those included in this systematic review by Li et al.,\textsuperscript{154} Cooley et al.,\textsuperscript{148} and
Mooney et al.\textsuperscript{153} suggest a broad symptom screening approach linked to evidence-based guideline recommendation may benefit patients and also be integrated into clinical workflows.

We noted patterns between studies by the outcomes measured. Process outcomes in an implementation study of CDS serve as a surrogate outcome due to its proximity to the intervention and may be easier to directly measure.\textsuperscript{79} Although the goal of CDS systems is improving patient outcomes, these may be challenging to measure and changes in patient outcomes may have additional confounding factors that need to be considered. In this systematic review, five of the ten included studies measured both process and patient outcomes, and three of these reported significant improvement in both measures. In these three studies, one studied a CDS system to improve management of anemia,\textsuperscript{158} another to improve management of fatigue,\textsuperscript{154} and the third to improve pain management.\textsuperscript{155} Two of these, Li et al and Bertsche et al, were integrated into the EHR, and these same two also include patient-reported data that was integrated into the CDS algorithm. The remaining two studies by Raj et al and Christ et al, where both process and patient outcomes were measured, reported no significant improvement in either. Both studies used CDS interventions that provided pain-management decision support.

Importantly, of the studies that measured patient outcomes (n=6), four reported significant improvement. The remaining two studies reported either no change or a non-significant trend toward improvement in the intervention group; no harm or worsening of symptoms was noted.

Integration into workflows should include EHR-integration,\textsuperscript{93} however, only three of the identified studies included EHR integration as a component of the CDS. EHR-integration, although it may be logistically challenging to implement, may improve some of the major workflow challenges that many have cited in clinical decision support.\textsuperscript{102,166} Kilsdonk et al. conducted a systematic review of barriers to implementing CPG-based CDS systems guided by
the human, organizational and technological factors framework.\textsuperscript{166} They found that along with utilizing a user-center design process and providing a recommendation at the exact time it is needed by the provider, the system should be integrated into the EHR or computerized provider order entry (CPOE) system to offer the best chance of success in providing useful information and improving patient outcomes. Of the three EHR-integrated studies\textsuperscript{154-156} two were recently published, suggesting that future research will continue to explore this important component of CDS development. In addition, of these three that included EHR-integration, two showed improvement in process outcomes and patient-reported outcome measures.\textsuperscript{154,155}

The geographic location of these studies is important to acknowledge. Although CDS has been highlighted as an important area of research focus by the National Academy of Medicine and other US institutions,\textsuperscript{102} as well as specifically within cancer-specific organizations, only three of ten studies were conducted in the US. This highlights an important gap which may be related to the complex healthcare system of the US and specific challenges of achieving the Meaningful Use goals of interoperability and health information standards, an important contributor to CDS success and sustainability.\textsuperscript{167,168}

Finally, all included studies reported using guidelines to inform the CDS recommendation. This is important and promising, as current recommendations include provision of evidence-based care as a necessary component of CDS.\textsuperscript{134,135}

**Limitations of this study**

There are some limitations to acknowledge within this systematic review. Although we conducted our literature search in multiple databases, it is possible that we missed relevant studies that may be indexed elsewhere. Similarly, grey literature was not included in the
literature search, which may have limited the inclusion of pilot studies, QI initiatives, or studies with negative findings.

Another limitation is the lack of a singular definition for CDS. We defined CDS broadly in our search, including terms such as “expert system” and “decision aid”, however, we may have missed studies where CDS was the intervention and would have met our definition criteria, but the authors used other terms. Although the informatics literature clearly states the technology-based definition, the clinical arena is sometimes ambiguous and includes a broad range and fast-paced integration of CPOE, order alerts, and other automated approaches to guide clinical decision making. In addition, these initiatives may occur in clinical practice as quality improvement (QI) initiatives that inform iterative updates to EHR-workflow. They may therefore not be published in a peer-reviewed journal or the clinical team leading the QI initiative may not include publication as part of their project. This highlights the importance of rigorous science to inform implementation studies as well as dissemination as a critical component of implementing initiatives to improve care delivery. Both dissemination and implementation should be encouraged across the landscape of quality improvement and assurance projects within healthcare settings.

Finally, we excluded paper-based CDS as the purpose of this study is to understand how technology can improve care delivery. As we move toward learning healthcare systems and interoperability goals, it is imperative that strategies to improve clinical decision making, such as CDS, be developed in an electronic format. It is possible, however, that these excluded studies may have been electronically-based but did not explicitly state that they were using automation or electronic strategies.
Conclusion

This study highlights the available evidence related to CDS that have been used in cancer settings to guide therapeutic decision making. Few studies were identified, signifying an important gap that needs to be addressed in future research. The studies that we identified had wide variability in their study setting, design and outcome measures. Encouragingly, all studies prompted a guideline-informed recommendation to the clinician, and more recent studies incorporated patient-reported information, supporting current initiatives toward standardized assessment of PROs and guideline-based interventions.169,170 Future research should focus on continuing to develop CDS that are usable, provide recommendations that are informed by CPGs to clinicians, are interoperable and integrated into the EHR, and ultimately impact upon and improve patient outcomes.
Chapter Three: Guideline Concordant Care for Prevention of Acute Chemotherapy-Induced Nausea and Vomiting in Children, Adolescents, and Young Adults

The study in Chapter Three addresses the second aim of the dissertation in a retrospective cohort study of patients less than 26 years of age who received emetogenic chemotherapy to determine the rate of guideline concordant care and to identify factors associated with receipt of guideline concordant care.

Abstract

Background: Chemotherapy-induced nausea and vomiting (CINV) is a common treatment-related adverse effect in children, adolescents and young adults with cancer that impacts treatment adherence and quality of life. Prescribing guideline-recommended anti-emetics is an effective strategy to prevent CINV. However, the rate of guideline concordant care (GCC) is not well-understood.

Methods: Using electronic health record data from 2016 through 2018, a retrospective single-institution cohort study was conducted to investigate how often patients less than 26 years of age receive GCC to prevent CINV prior to administration of emetogenic chemotherapy. GCC was defined from the Pediatric Oncology Group of Ontario guideline for patients < 18 years and the American Society of Clinical Oncology guideline for those ≥ 18 years. Independent variables included: sex, age, insurance status, race, ethnicity, cancer type, chemotherapy regimen, clinical setting (adult or pediatric oncology), level of emetogenicity, and patient location (inpatient or outpatient). Predictors of GCC were determined using multiple logistic regression.

Results: Of 180 eligible patients, 65 (36.1%) received GCC. In multivariable analysis, being treated in adult oncology (aOR: 14.3, CI95: 5.3 – 38.6), with a cisplatin-based regimen (aOR: 3.5,
CI\textsubscript{95}:1.4 – 9.0), solid tumor diagnosis (aOR: 2.2, CI\textsubscript{95}: 1.0 – 4.8), and commercial insurance (aOR: 2.4, CI\textsubscript{95}: 1.1 – 5.2) were associated with significantly higher likelihood of receiving GCC.

Conclusions: Patient clinical and sociodemographic, as well as provider characteristics were all identified as being associated with receiving GCC for prevention of CINV in children, adolescents, and young adults receiving emetogenic chemotherapy. These findings can inform current efforts to optimize implementation strategies for supportive care guidelines by focusing on multi-level factors.

Background

Symptom management for children, adolescents and young adults with cancer is important; it reduces adverse effects of treatment, keeps treatment on schedule by reducing delays, and improves overall patient outcomes.\textsuperscript{171} Chemotherapy, a common treatment modality for cancer, often causes nausea and vomiting, which like other treatment-related adverse effects, can cause treatment delays and significantly reduce quality of life.\textsuperscript{172-174} It is also one of the most feared adverse effects of chemotherapy.\textsuperscript{26,38,172} It is therefore important to prevent and manage chemotherapy-induced nausea and vomiting (CINV), which can be achieved through the use of rigorously-developed evidence-based clinical practice guidelines.

Provision of guideline concordant care (GCC) for the prevention of CINV requires knowledge about treatment-specific factors. Certain chemotherapeutic agents or combinations of chemotherapy have a higher emetogenic potential, and guidelines have been developed to classify the emetogenic potential of the most common chemotherapies.\textsuperscript{175,176} Guideline recommendations are based on these classifications and are available for pediatric and adult cancer patients.\textsuperscript{64,176-178} Although some patients may still experience symptoms of CINV with
appropriate prophylaxis, studies have shown that administering prophylactic regimens concordant with published guidelines can significantly reduce or control symptoms for patients who receive moderately or highly emetogenic chemotherapy.63,179,180

Despite the availability of effective medications and rigorously-developed guidelines to help prevent and treat CINV specifically in pediatric oncology settings, there is wide variation in the provision of anti-emetic medications. One study found that 78% of sites self-reported a standardized approach to prophylaxis, however, only 41% reported that the approach was consistent with GCC.18 Some reasons for not providing GCC include lack of awareness of the guideline, concerns about drug interactions, specifically neurokinin-1 receptor blockers, and contraindications for dexamethasone use due to concomitant medication concerns or adverse effects of steroids.181-183 Furthermore, the guidelines may be viewed as less robust or trustworthy specifically in children, because the data for guideline development are often extrapolated, at least in part, from adult data.184,185

The negative effects of this inconsistency are important, as children and adolescents with cancer may be undertreated or inappropriately prescribed medication leading to worse CINV symptoms than in older patients. Studies of adults with cancer have reported better CINV control, and a recent pooled synthesis of adult symptoms reporting a prevalence of 40% for nausea and 27% for vomiting.186 In contrast, for children and adolescents, this number is frequently cited higher, especially chemotherapy-induced nausea. One study of school-aged children with cancer found that 80% of children with cancer reported nausea a week after chemotherapy and nearly half of parents reported nausea that caused significant bother.174 Vomiting prevalence ranged from 5 – 41% and notably, both symptoms are increasingly reported up to one week following chemotherapy administration.174,187
Symptom management, specifically prevention of CINV, is imperative to maximize patient outcomes in cancer treatment. Though guidelines are available for children, adolescents, and young adults with cancer, it is not currently known how often they receive guideline-recommended care and what factors are associated with receiving this care. Therefore, the purpose of this study was to describe the proportion of pediatric, adolescent, and young adult patients receiving highly-or moderately-emetogenic chemotherapy, to assess who prophylactically received guideline concordant antiemetic regimen to prevent acute CINV, and to identify potential predictors of guideline concordant antiemetic prophylaxis treatment.

Methods

Data Source

A retrospective cohort study using the electronic health record (EHR) data of a large, urban hospital that includes a stand-alone children’s hospital, inpatient and outpatient cancer clinics all within an NCI-designated Comprehensive Cancer Center was conducted. This study was approved by the Institutional Review Board at Columbia University; a waiver of HIPAA authorization was granted (IRB-AAAR9461).

Sample

Subjects 26 years of age or younger who received chemotherapy classified by guidelines as either highly-emetogenic (HEC) or moderately-emetogenic (MEC)\textsuperscript{175,178} were included in the analysis (Appendix B). All chemotherapy classified by the 2011 antiemetic classification pediatric guideline\textsuperscript{175} as HEC or MEC were included because this guideline is broader in its inclusion of emetogenic chemotherapy. For patients > 18 years, the emetogenic classification of the chemotherapy regimen was confirmed as either HEC or MEC according to the American
Society of Clinical Oncology (ASCO) guideline. If it did not, they were excluded from the primary analysis.

The Tripartite Request Assessment Committee (TRAC) of NewYork-Presbyterian Hospital, Columbia University Medical Center, and Weill Cornell Medical College has been established to share data across institutions for clinical care, operations, quality improvement, and research. Through this data request system, all patients were identified who received these chemotherapeutic agents between January 1, 2016 and December 31, 2018. Computerized provider order entry for all chemotherapy was the institutional mode of prescribing chemotherapy.

Although all clinical settings where eligible patients were treated are within the same hospital system, the pediatric and adult oncology programs operate as distinct operations and utilize their own internal care pathways to provider cancer treatment and supportive care. Both pediatric and adult oncology divisions have developed recommendations for anti-emetic selection when ordering chemotherapy medications, however, the recommendations may or may not be based on guidelines and prescribers can opt-out of providing the recommended medications. The development process for these anti-emetic prescribing care pathways does not include a standardized methodology that is consistently and routinely updated.

From this patient list, MB logged into the EHR of each patient to confirm eligibility and abstract the variables of interest for the dataset; the EHR domains of interest for the abstracted variables are listed in Appendix D. First, the date of the first chemotherapy encounter for each individual patient was confirmed. This was the episode of interest, and each patient was eligible to contribute one episode. Patients who had received prior chemotherapy at another institution or who previously received a regimen that was not classified as HEC or MEC were excluded.
Patients with a recurrence of their disease were included if the episode was the first chemotherapy administration for the recurrence. For patients who received an eligible combination of chemotherapy, the two chemotherapeutic agents had to be administered within 7 days of each other.

**Antiemetics**

The medication administration record was accessed through the same procedure of institutional data request, and anti-emetic administered to the patient during the chemotherapy encounter were identified. The list of anti-emetics was developed from a review of CINV guidelines both for prevention of acute CINV, treatment of refractory CINV, and management of anticipatory CINV (Appendix C). Guideline-recommended anti-emetics were only requested if they were available through the hospital formulary during the study period.

Anti-emetic administration was abstracted both from the automatically-generated list through the institutional request, as well as confirmatory EHR review. In the EHR, all medication administration records were assessed to ensure any administration, even if the patient was in a different location from where the chemotherapy was administered, was captured. For example, if a patient received ondansetron in the outpatient setting and was admitted for chemotherapy to the inpatient setting, this would be captured during the review and abstraction procedures.

Each patient encounter was assessed to identify if they received the following classes of antiemetic: neurokinin-1 receptor blockers (NK1RAs), 5HT3 serotonin receptor antagonists (5HT3-blockers), and dexamethasone prior to the chemotherapy encounter. To be considered for evaluation of GCC, antiemetics needed to be prescribed and administered prior to the administration of chemotherapy. NKIRAs included fosaprepitant and aprepitant, which were the
NK1RAs on the hospital formulary, and 5-HT3 serotonin receptor antagonists included ondansetron, granisetron, and palonosetron. Anti-emetics classified as “other” were also abstracted (Appendix C).

Clinical and demographic characteristics

Independent variables (e.g. clinical, system-level, and sociodemographic) were abstracted from the EHR as potential factors associated with receipt of guideline-recommended prevention of CINV. Clinical factors included: primary oncologic diagnosis (i.e. leukemia, lymphoma, solid tumor, or central nervous system (CNS) tumor), cancer recurrence, chemotherapy regimen, emetogenicity of chemotherapy regimen, and co-morbidities at the time of chemotherapy initiation. System-level factors included: location of chemotherapy administration (inpatient, outpatient), and clinical setting (pediatric, adult oncology). Sociodemographic characteristics included: age at the time of chemotherapy administration, categorized initially as 0 – 5 months, 6 months – 11 years, 12 – 17 years, 18 - < 26 years, and then dichotomized as 0 – 11 years and 12 – 26 years. Race and ethnicity were also collected, along with primary insurance status that was categorized as commercial/private insurance, governmental (i.e., Medicaid/Medicare), or uninsured/self-pay. Sociodemographic characteristics were abstracted from the patient demographic section within the EHR; if unavailable or not listed in that section of the EHR, MB reviewed the patient-completed intake forms that are scanned into the EHR and archived with other paper documents. In addition, insurance status at the time of chemotherapy encounter was confirmed by reviewing the social worker intake form, also located in the EHR.
Primary outcome

The primary outcome for this study was receipt of guideline concordant care for the prevention of acute CINV for patients receiving highly- or moderately-emetogenic chemotherapy. Patients were stratified by age, according to the published guideline recommendations for the prevention of acute CINV at the time of this study, one for children and the other for adults.

For the patients < 18 years of age, GCC was defined using The Pediatric Oncology Group of Ontario guideline for prevention of acute CINV in children receiving chemotherapy; the guideline was updated in 2013 and again in 2017.61,64 This guideline, consistent with other guidelines for CINV prevention, recommends provision of a 5HT3-blocker, a corticosteroid, specifically dexamethasone, and a NK1RA to prevent CINV in children and adolescents receiving HEC.64 In the 2013 guideline, NK1RAs were not recommended for children under the age of 12 years due to limited pediatric data. The 2017 guideline, however, expanded the age limit anyone older than 6 months of age. For patients receiving MEC, this CPG recommends administration of a 5HT3-blocker and corticosteroid, specifically dexamethasone. For patients unable to receive dexamethasone, the recommendation supports using an alternative antiemetic, specifically metoclopramide, nabilone, or prochlorperazine.

For young adults, defined in our study as 18 < 26 years, GCC was defined from the ASCO guideline, which similarly recommends triple therapy with a 5HT3 blocker, NK1RAs, and dexamethasone for patients receiving HEC.178 A recent update in 2017 added olanzapine to this recommendation.176,190 This medication has not yet been recommended for pediatric patients. For patients receiving MEC, the recommendation is identical to the pediatric recommendation: 5HT3-blocker and corticosteroid, specifically dexamethasone. Because both
the pediatric and adult guideline were updated in 2017, and our study includes this year, GCC was defined from the guideline previously published (e.g. for pediatric, 2013 and for adults, 2011) given that the implementation of guidelines is often delayed.\textsuperscript{191}

**Secondary Outcomes**

Our primary outcome was defined strictly from the guidelines which include dexamethasone as a component of GCC. However, in clinical practice there may be contraindications or hesitation to prescribe certain classes of antiemetics. To account for these differences, a secondary analysis was conducted to describe patients who receive dexamethasone and NK1RA separately.

**Statistical Analysis**

Descriptive statistics were computed to assess for the frequency of clinical, system-level, and sociodemographic characteristics as well as for the primary and secondary outcomes. Certain variables were collapsed into binary outcomes, specifically race (white, non-white), ethnicity (Hispanic, non-Hispanic), age (< 12 years, \( \geq 12 \) years), cancer type (solid tumor, all other cancers), and chemotherapy regimen (cisplatin-based, non-cisplatin based) for bivariate and multivariable analyses. Associations between the predictors and primary outcome, guideline-recommended anti-emetic regimen were calculated using Chi-square tests and logistic regression. Variables with a p-value < 0.1 in the bivariate analysis were included in the multivariable logistic regression model and independent variables with a p-value of < 0.05 were included in the final model. Odds ratios and 95\% Wald confidence intervals were reported.

Chi-square tests were used to assess for correlation between age and provider setting, and p-values were reported. Testing for interaction was conducted using likelihood ratios (LR) test.
between provider setting and insurance status. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Through the institutional data pull from the TRAC system, 295 patients were identified; After review of each of these charts, 115 were excluded due to not having cancer (n= 47), chemotherapy dosing not qualifying as HEC or MEC (n= 18), receiving prior chemotherapy at another institution (n= 25), and duplicate patient records (n=20). Table 3.1 describes the characteristics of the 180 patients included in our final sample. A slight majority (54%) were male, 41% had commercial insurance at the time of treatment, 61% were white and 63% were non-Hispanic. The largest age groups were the 6m-7y (37%) and young adults >17y (40%). Most were seen by pediatric oncology providers (73%), in the inpatient setting (73%). The most common cancers were solid tumor (41%) and leukemia (24%), and most received HEC (71%) with 19% of the sample receiving cisplatin-based regimens. Most patients were undergoing their first treatment (85%) and were not being treated for relapsed disease. Seventy-four percent (n=133) did not have any co-morbid conditions at the time of chemotherapy administration. Of those who did, asthma (n=8), post-organ transplantation (n=8), and congenital syndromes (n=10) were the most common conditions.
Table 3.1: *Summary of Sample Characteristics (n=180)*

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98 (54.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>82 (45.6%)</td>
</tr>
<tr>
<td><strong>Insurance (primary)</strong></td>
<td></td>
</tr>
<tr>
<td>Medicaid/Medicare</td>
<td>103 (57.2%)</td>
</tr>
<tr>
<td>Commercial</td>
<td>73 (40.6%)</td>
</tr>
<tr>
<td>Self-pay/non-insured</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
</tr>
<tr>
<td>0 – 5M</td>
<td>5 (2.8%)</td>
</tr>
<tr>
<td>6M – 11Y</td>
<td>67 (37.2%)</td>
</tr>
<tr>
<td>12Y – 17Y</td>
<td>36 (20%)</td>
</tr>
<tr>
<td>18Y &lt; 26Y</td>
<td>72 (40%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>110 (61.1%)</td>
</tr>
<tr>
<td>Black</td>
<td>32 (17.8%)</td>
</tr>
<tr>
<td>Asian</td>
<td>13 (7.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>25 (13.9%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>114 (63.3%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>64 (35.6%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>132 (73.3%)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>48 (26.7%)</td>
</tr>
<tr>
<td><strong>Provider setting</strong></td>
<td></td>
</tr>
<tr>
<td>Pediatric Oncology</td>
<td>132 (73.3%)</td>
</tr>
<tr>
<td>Adult Oncology</td>
<td>48 (26.7%)</td>
</tr>
</tbody>
</table>
Table 3.1: *Summary of Sample Characteristics (n=180) (cont’d)*

<table>
<thead>
<tr>
<th>Emetogenicity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly-emetogenic (HEC)</td>
<td>127 (70.6%)</td>
</tr>
<tr>
<td>Moderately-emetogenic (MEC)</td>
<td>53 (29.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>12 (6.7%)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>34 (18.9%)</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>12 (6.7%)</td>
</tr>
<tr>
<td>Dactinomycin</td>
<td>21 (11.7%)</td>
</tr>
<tr>
<td>Other HEC</td>
<td>48 (26.7%)</td>
</tr>
<tr>
<td>MEC</td>
<td>53 (29.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid tumor</td>
<td>73 (40.6%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>48 (26.7%)</td>
</tr>
<tr>
<td>CNS</td>
<td>16 (8.9%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>43 (23.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>First occurrence</td>
<td>153 (85%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>27 (15%)</td>
</tr>
</tbody>
</table>

Of the 180 patients, 36% received age-appropriate, guideline concordant anti-emetics prior to the administration of chemotherapy. In the bivariate analysis (table 3.2) five independent variables were found to be significantly associated with receiving GCC (table 3.3). Race was not included due to the large number of patients with “unknown” status (14%). In the multivariable model, four variables: provider type, primary insurance, tumor type, and chemotherapy regimen, were included and remained significant at the 5% level (table 3). Age group was not included in
the multivariable analysis as it was highly correlated with provider type (Chi-square: 43.6,
p<.0001).

Table 3.2: *Bivariate Analysis of Independent Variables and Outcome: Guideline Concordant Care Received*

<table>
<thead>
<tr>
<th></th>
<th>GCC Received (n)</th>
<th>Not Received (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>65</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td>.90</td>
</tr>
<tr>
<td>Male</td>
<td>35</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td><strong>Insurance (primary)</strong></td>
<td>.02*</td>
<td>.02*</td>
<td></td>
</tr>
<tr>
<td>Non-commercial</td>
<td>31</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>34</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td><strong>Age group: young vs. old &gt;12y</strong></td>
<td>.03*</td>
<td>.03*</td>
<td></td>
</tr>
<tr>
<td>0 – 11Y</td>
<td>19</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>12Y &lt; 26Y</td>
<td>46</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>.01**</td>
<td>.01**</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>31</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Non-White</td>
<td>34</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>.50</td>
<td>.50</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>39</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>26</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>.20</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>44</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>21</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td><strong>Provider setting</strong></td>
<td>.0001*</td>
<td>.0001*</td>
<td></td>
</tr>
<tr>
<td>Pediatric Oncology</td>
<td>29</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Adult Oncology</td>
<td>36</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Emetogenicity</strong></td>
<td>.33</td>
<td>.33</td>
<td></td>
</tr>
<tr>
<td>Highly-emetogenic (HEC)</td>
<td>43</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Moderately-emetogenic (MEC)</td>
<td>22</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.2: Bivariate Analysis of Independent Variables and Outcome: Guideline Concordant Care Received (cont.)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Bivariate Analysis</th>
<th>Reduced Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider setting</td>
<td>OR: 14.3 (5.3 – 38.6, p&lt;.0001)</td>
<td>aOR 10.9 (4.8 – 25.0, p&lt;.0001)</td>
</tr>
<tr>
<td>Age</td>
<td>OR: 1.6 (.64 – 4.0, p=.31)</td>
<td>*</td>
</tr>
<tr>
<td>Primary Insurance</td>
<td>OR: 2.4 (1.1 – 5.2, p=.02)</td>
<td>aOR: 2.3 (1.1 – 4.9, p=.03)</td>
</tr>
<tr>
<td>Solid tumor vs. other cancer</td>
<td>OR: 2.2 (1.0 – 4.8, p=.04)</td>
<td>aOR: 2.3 (1.1 – 5.0, p=.03)</td>
</tr>
<tr>
<td>Cisplatin-based therapy</td>
<td>OR: 3.5 (1.4 – 9.0, p=.01)</td>
<td>aOR: 3.6 (1.4 – 9.3, p&lt;.01)</td>
</tr>
</tbody>
</table>

*Excluded from reduced model

* Significant at the 5% level, included in multivariable logistic regression

** Excluded from multivariable regression due to 14% “unknown” status
Sensitivity Analysis and Interactions

A sensitivity analysis was conducted to explore the relationship between emetogenicity and other independent variables. Bivariate analysis between emetogenicity and all independent variables revealed associations with provider setting and age. Pediatric oncology patients were more likely to receive highly-emetogenic chemotherapy than adult oncology patients (p=.07), and younger patients < 18 years were more likely to receive highly-emetogenic chemotherapy than patients ≥ 18 years (p = .08). All other associations were not significant at the (p < .10) level.

In addition, we assessed for interaction between provider setting and insurance status using the LR test. We ran two models, the reduced and full. In the full model -2L Log L: intercept=124.289, Intercept and covariates = 103.605; and in the reduced: -2L log L: intercept 124.289, intercept and cov = 105.368. Since the test statistic (G2) = 105.368 – 103.605 is < the critical value for X2 df = 2, .05 = 5.991. Therefore, we do not have sufficient evidence to support that insurance status modified the association between provider type and GCC at the .05 level of significance.

Secondary Outcomes: Antiemetics by Drug Classification

Ninety-eight percent (n=177) of the total sample had received a 5HT3-blocker; 44% (n=80) received dexamethasone, and 26% (n=46) received a NK1RA. Receipt of dexamethasone was reported by tumor type, acknowledging the clinical limitation of administering steroids to patients with brain tumor, leukemia, and lymphoma, because they often receive steroids as a component of anti-tumor treatment. A sub-group analysis on patients with solid tumors, therefore
with no overt contraindication or concomitant concerns for dexamethasone, identified 62% (45/73) of patients received dexamethasone.

Receipt of NK1RA for patients receiving HEC was also examined by age group. None of the youngest age group and 10% of the 7m – 11y group received a NK1RA. In older patients for whom the guideline recommends NK1RAs, of those 12 – 17y of age, 26% received NK1RAs whereas 64% of the oldest group ≥ 18 years received NK1RAs, consistent with GCC. Overall, 49% (35/71) of patients 12 years and older received a NK1RA. Finally, 35% (n=64) of the sample had received additional anti-emetics prior to their chemotherapy. There was wide variety in the medication(s) given, and the most commonly prescribed was lorazepam (n=52).

Discussion

Our study found that in a cohort of patients ≤ 26 years of age receiving emetogenic chemotherapy, 36% received guideline concordant anti-emetic prophylaxis. To our knowledge, this is the first study to describe the rate of GCC in a pediatric and young adult patient population. This is an important finding that highlights both the importance of guideline-based supportive care in children, adolescents, and young adults with cancer but also the challenges in prescribing both to younger patients and for specific types of cancers.

Our study finding of a low rate of GCC is consistent with the limited literature describing GCC in pediatric oncology symptom management. A multi-institutional survey conducted through the Children’s Oncology Group found that less than half of the 36 participating institutions followed institution-specific guidelines, with only 28% following the CPG endorsed by the Children’s Oncology Group.18 Our results provides further knowledge about the patient-level rate of guideline concordant care. In addition, our study found that patients treated in adult
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oncology were significantly more likely to receive GCC. Current initiatives, such as the ongoing trial through the Children’s Oncology Group (NCT02847130), aim to understand both the barriers and facilitators to implementing supportive care guidelines in pediatric cancer settings and to improve how well these guidelines are understood by healthcare providers. Our study supports the need to conduct this and future research in this area to increase guideline uptake in pediatric cancer settings.

The evidence-base for the development of pediatric-specific guidelines, is often based, at least in part, on data from studies in adults or in rigidly-defined populations. In CINV studies, for example, much of the efficacy data for antiemetics comes from specific populations, such as those receiving cisplatin-based therapy. Our study found that patients receiving cisplatin-based regimens were significantly more likely to receive GCC, suggesting that awareness about the need for optimized prophylaxis is heightened in this population, perhaps related to the evidence-base from which the data comes. Specifically, in our study only 14% of patients receiving dactinomycin and 14% of patients receiving combination chemotherapy classified as HEC, received GCC. Future interventions that increase awareness of the classification of chemotherapies are therefore warranted.

In addition, because much of the evidence-base for guideline development comes from data in adults, it is important to consider the distribution of cancer in adults compared with children and adolescents. Adults have a higher prevalence of solid tumors, and prescribing dexamethasone does not come with the same challenges as in the more prevalent pediatric cancers, leukemia and CNS tumors. Specific issues with prescribing dexamethasone include concomitant dosing of additional corticosteroids, such as prednisone which is commonly part of the anti-tumor regimen, or the side effect profile of corticosteroids, including behavioral,
infectious, and bone-related toxicities. Importantly, leukemia is the most common childhood cancer, and this highlights some of the challenging is providing appropriate antiemetic control to younger patients. Guideline-recommended interventions may not, or cannot in some cases, be adhered to due to protocol or clinical restrictions.

Similarly, there are known pharmacokinetic interactions of NK1RAs with specific chemotherapies and other commonly-used medications in cancer management. These include clinically significant pharmacologic interactions between cyclophosphamide IV, and 28% of the patients included in this study received this as a component of their regimen. In addition, adverse events related to a drug interaction between a NK1RA and other medications were described, including anthracyclines and ifosfamide, and 28% of the patients included in this study received one of these chemotherapeutic drugs. NK1RA are an important part of CINV management; however, it is important to consider their side effect profile and interactions with commonly-used chemotherapy.

The 2013 pediatric guideline recommends that patients who cannot receive dexamethasone or an NK1RA as recommended should receive secondary medications as prophylaxis, and the 2017 guideline similarly recommends palonosetron, a specific 5HT3-blocker, that has demonstrated increased efficacy in pediatric settings. These are limited optimal prevention strategies for younger patients, and some of these medications having significant side effects such as extrapyramidal effects and sedation. In fact, a negligible number (n=13) of patients in this study received one of the three recommended medications for patients who are unable to receive dexamethasone. This supports the need for a more robust evidence-base of pediatric-specific guidelines as well as rigorous testing of newly-approved medications specifically in pediatric patients.
Recent federal regulations highlight the need for increased drug development and testing in children and adolescents. Prior to 1997, few drugs were approved for use in children; since the Food and Drug Administration (FDA) Modernization Act, pediatric efficacy and safety data has been encouraged and sometimes required in drug development and approvals. Exemptions have been allowed especially for cancer drugs due to the relative rare status of pediatric cancer. A recent update to the regulation, however, will remove the exemption and require pediatric testing regardless. Recent statements from the FDA acknowledge and state support for improved pharmacologic interventions with supporting evidence base for children.

Our study also identified disparities in the delivery of GCC. Patients with primary commercial insurance were significantly more likely to receive GCC (p=.02). This disparity in CINV management should be explored across multiple institutions to better understand and validate this finding. A previous study of adult breast cancer patients described disparities in receipt of GCC related to social determinants, reporting that black women were 11% less likely to be prescribed NK1Ras compared with white women. However, in our study, over 70% of the patients were inpatient for their chemotherapy, and in general, individual medications are not charged but are bundled. It is possible, therefore, that this disparity is a proxy for other sociodemographic disparities that were not identified in this single-institution study. Larger studies in multiple settings are therefore needed to further explore disparities in delivering GCC for CINV prevention and management.

Multiple factors significantly associated with receiving GCC were identified. Multi-level implementation strategies have been cited in the literature as an effective mechanism to address patient-, provider-, and system-level barriers to guideline implementation. Specifically through the Expert Recommendations for Implementing Change (ERIC), strategies such as clinical
decision support integrated into the electronic health record, audit and feedback, approaches to change organizational climate, and collaborations may be useful to improve cancer care delivery across multiple settings.\textsuperscript{200} These approaches can help to identify patient-level clinical and sociodemographic factors and provide guideline-based decision support. Other strategies, such as enhanced education and discussions to increase awareness of and develop quality improvement strategies that clinicians feel comfortable adopting and implementing may also be effective and should be explored further.\textsuperscript{201} Certainly, a multi-level approach to improve guideline-based care is needed to address cancer symptom management.

**Strengths and Limitations**

This study has some strengths and limitations worth discussing. First, this is a single-institution study, thus limiting the generalizability of the findings. However, because of the patient-level data from the EHR, the reliability of these data is strong, which is a common challenge of larger, insurance database studies.

Another limitation is our inability to appropriately assess for disparities, specifically by race as previously cited in the literature due to 14\% of patients having “unknown” status in the EHR. Capturing patient-level sociodemographic data is an ongoing challenge for many healthcare systems, and the Institute of Medicine and other governmental agencies continues to support the importance of these data in healthcare disparities research, quality improvement initiatives and quality measures.\textsuperscript{202,203} These and local initiatives should be encouraged to improve the accuracy of data reporting.

Finally, due to our limited sample size, relationships between other factors and GCC may not have been identified with the potential for a type 2 error. Significant relationships between
multiple factors and GCC, however, were identified, suggesting that these relationships are internally valid. This work would be strengthened by broadening the study both to multiple settings or institutions and increasing the sample size.

Future implications

The findings from this study contribute important knowledge to the evidence base of supportive care guideline implementation and adherence in pediatric, adolescent, and young adult settings. Data such as this can be used as a benchmark to measure initiatives to increase provision of GCC. Currently, ongoing initiatives at local and national levels aim to understand barriers to providing GCC to these patients and to develop interventions to improve rates of GCC. Our study supports the need for both provider- and patient-level interventions. Policy implications are also important to acknowledge; children and adolescents are frequently underrepresented in drug safety data. The U.S Food and Drug Association acknowledges this as a limitation and incentivizes pharmaceutical companies to include a pediatric-specific component of new drug applications;\textsuperscript{199,204} however, there is still clearly a paucity of pediatric-specific data that is generalizable across multiple clinical and sociodemographic settings.\textsuperscript{205} Similar to prior publications about the importance of guideline development in pediatric oncology, increasing the evidence base to develop these guidelines should continue to be a focus.

Conclusion

In summary, in this retrospective cohort study of children, adolescent, and young adults with cancer and receiving emetogenic chemotherapy, an overall low rate of GCC was found. Factors associated with receiving GCC include provider specialty, chemotherapy regimen, type of insurance, and type of cancer diagnosis. Future implementation strategies should focus on
these factors to improve rates of GCC. In addition, further research is needed to define alternatives for antiemetic regimens when certain classes, specifically NK1RAs and dexamethasone, cannot be given. Federal and pharmaceutical funding should support development of pediatric medications.
Chapter Four: Completeness, Concordance, and Heterogeneity of Documentation of Chemotherapy-Induced Nausea and Vomiting in Children and Young Adults with Cancer

The study in Chapter Four addresses the third aim of the dissertation in a mixed-methods study to describe the completeness, concordance, and heterogeneity of the EHR documentation about CINV in patients less than 26 years of age who received highly-emetogenic chemotherapy.

Abstract

Objective: To describe the completeness, concordance, and heterogeneity of the electronic health record (EHR) documentation of chemotherapy-induced nausea and vomiting (CINV), to map the concept of CINV using clinical terminologies, and to develop a post-coordination expression.

Methods: A mixed-methods study was conducted to examine the EHR of children, adolescents, and young adults who recently received highly-emetogenic chemotherapy. In Phase I, we described how often CINV was assessed and reported by prescribers and registered nurses (RNs) and the concordance by clinician type and by ICD-10 codes. In Phase 2, we utilized the terms identified in Phase I and from validated CINV tools to map the concept of CINV through SNOMED-CT and then UMLS and develop a post-coordinated approach for phenotyping patients with CINV.

Results: 127 patients’ EHRs were reviewed, and of these a total of 870 patient notes were reviewed. Documentation of CINV assessment by prescriber was present in 75% of patients, and by RNs was present in 58% of patients. Of the 60 encounters where both prescriber and RN documented an assessment, 72% agreed on the presence/absence of CINV. We mapped CINV first through SNOMED-CT and subsequently through UMLS to incorporate other terminologies, mainly ICD-10 and Rx—NORM. Post-coordinated expression of CINV was applied to the
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documentation from the EHR and partially identified patients’ CINV status 85% for prescriber and 100% for RN documentation, and completely identified patients’ CINV status 21% for prescriber and 38% for RN documentation.

**Discussion and Conclusion:** Although most patients receiving highly-emetogenic chemotherapy have a documented assessment of CINV, most patients had incomplete and discordant documentation of CINV, most commonly, temporality and severity were not documented. In addition, heterogeneity of documentation location was noted. Mapping the terms through UMLS informed post-coordination expression of CINV to improve capture of the presence or absence of CINV but did not improve the completeness of the documentation, specifically related to severity and temporality of the symptom.

**Background**

**Electronic Health Record Data**

Electronic health records (EHRs) are now ubiquitous in healthcare, and as of 2017, 94% of hospitals eligible for the Medicare and Medicaid EHR Incentive Program used their EHR data to measure hospital processes and inform clinical practice. There are ever-increasing amounts of data available through EHR records, and methods to interpret and utilize these data for secondary use of these data has been widely explored. EHR data quality is a well-described challenge to secondary use, and common challenges include lack of completeness, correctness, concordance, plausibility, and currency of the data. EHR data quality reported in the literature varies widely depending on the clinical concept of interest as well as healthcare system- or institutional-level variability.

Two dimensions of data quality, completeness and concordance of EHR data are commonly cited as challenges when researchers, clinicians, and administrators use these data to
characterize patients. For the purpose of this study, completeness is defined as patient-level documentation that is present and available in the EHR, and concordance is defined as the agreement between elements, observations or values that are documented in the EHR. Incomplete data occurs when data is not documented or only partially-documented. Incomplete data may be related to the pertinent negatives that are not routinely documented in clinical care. However, one cannot assume that because the data is not present, clinical observations were not noted by the clinician who is documenting and/or experienced by the patient. Another reason for incomplete data may be due to a lack of integration for patient-reported outcomes or preferences in the EHR system. If available and integrated into the EHR, these data can increase the completeness of data and therefore, utility of patient-level data. Currently, these data are not routinely integrated into the EHR system.

Discordance in EHR data may occur when multiple providers document differing observations in the EHR or when factors, such as the timing of a clinical event or the clinician workflow, cause a provider to document one observation in one location of the EHR and a different observation in another location. In addition, both incomplete and discordant data can also be due to errors in documentation. Understanding the completeness and concordance of data in the EHR provides a baseline assessment of data quality that is needed prior to harnessing EHR data for clinical research purposes.

Another challenge with EHR data is heterogeneity, often related to the multitude of data types that may be available in the EHR. For example, a clinical data warehouse may access data from multiple systems and locations with the EHR, and then need to integrate structured and unstructured data into an understandable format for future use to measure patient and process
Heterogeneity within EHR data causes challenges when clinicians, administrators, and researchers want to identify and analyze non-structured data and free text from the EHR.

Strategies to assess, utilize, and interpret EHR data have been described, and historically required manual review by clinical experts and knowledge engineers, a time-consuming and costly process. Recently, more efficient methods have been developed and refined including automated methods to phenotype, or characterize, common patient characteristics from EHR data. Phenotyping can identify patients with common comorbidities or risk factors who may benefit from interventions to improve patient outcomes. Phenotyping can be conceptualized from two aspects, top-down knowledge engineering and bottom-up learning from the data. Phenotyping methods often utilize prior knowledge engineering and concurrently integrate new knowledge from structured and unstructured EHR data. To phenotype a common characteristic from EHR data, however, it is important to assess and understand the data quality.

Phenotyping algorithms, or the pathway to identify the cohort of interest, commonly depend on controlled terminologies. Controlled terminologies have been developed to allow for meaningful representation of data using symbols; they support “the capture, storage, manipulation, and retrieval” of information in a way that preserves the original meaning of the data. Multiple taxonomies, or clinical terminologies, exist to cover the breadth and depth of health-related information that is found in health insurance databases, electronic health records, genomic, and other health-specific databases.

The Systematized Nomenclature of Medicine -- Clinical Terms (SNOMED-CT), a commonly-used, standardized healthcare terminology is considered the most comprehensive in the world. Implementation of SNOMED-CT into EHR systems supports consistent, comprehensive representation of relevant clinical information which is necessary for reusing
EHR data in a single health system as well as supporting health information exchanges across systems. SNOMED-CT has numerous pre-coordinated expressions available that provide relevant contextual information about multiple health-related terms; figure 4.2 shows the diagram for the pre-coordinated term “chemotherapy-induced nausea vomiting.” In the absence of a pre-coordinated expression, however, a strength of SNOMED-CT is the ability to “post-coordinate” expressions by building terms together with modifiers and qualifiers. For example, in the absence of the pre-coordinated expression readily available in the EHR documentation, a post-coordinated expression can identify patients who have pre-defined terms, also called atoms, available in the clinical documentation to better identify patients with a specific characteristic. SNOMED-CT can be mapped to other common terminologies, such as the 1) International Classification of Diseases (ICD)-10 codes, a terminology used for reporting morbidity and mortality data to National Center for Health Statistics and the Centers for Medicare and Medicaid Services and for billing in healthcare systems; and 2) RxNorm, a standardized nomenclature for clinical drugs.

The Unified Medical Language System (UMLS) is a comprehensive system that brings together many of these terminologies (e.g. SNOMED-CT, RxNorm, ICD-10) to enable interoperability across systems. One specific UMLS knowledge source, the Metathesaurus, links terms and codes from multiple vocabularies and terminologies. UMLS is a helpful resource to organize and link terminologies, integrate them into algorithms, and develop patient-specific phenotypes or cohorts to identify associated predictors and mediators of disease. Ultimately, UMLS may be used to support development of phenotyping algorithms and prospective, predictive modelling interventions, such as clinical decision support (CDS) systems. UMLS is also useful to leverage existing data and conduct retrospective studies.
The predictive capabilities as well as the ability to harness already-existing EHR data to understand patient outcomes are important strengths of phenotyping EHR data, and data-driven phenotyping is a well-described methodology used to identify common diseases, such as chronic kidney disease, diabetes, or atrial fibrillation. To our knowledge, however, this approach has not been used to develop cancer-related symptom phenotypes.

Cancer Symptom Management

Symptom management is an integral component of high-quality cancer care, and appropriate identification and management of symptoms can improve patient-reported quality of life and reduce adverse effects of both disease and cancer-related treatment. One of the most common treatment-related symptoms is chemotherapy-induced nausea and vomiting (CINV), affecting up to 80% of cancer patients. Evidence-based guidelines have been rigorously developed both to classify the emetogenicity of chemotherapy and to provide recommendations to prevent and treat CINV. These guidelines offer treatment-, age-, and timing-specific recommendations that can be incorporated into a care pathway or algorithm. Despite the evidence that supports these guidelines, they are not always followed in clinical practice. There is wide variety on providing guideline-consistent care, and adherence to guidelines may be lower in pediatric settings. Barriers to guideline implementation have been described and are often classified by patient-specific, provider-specific, and system-level factors. In CINV prevention and management, barriers include difficulty appropriately identifying patients at risk for CINV, lack of systematic symptom screening for at-risk patients, and outdated or incomplete knowledge of the most up-to-date guideline, especially in children and adolescents as the guideline recommendations are often age-specific.
Significance and Purpose

The importance of CINV as a symptom\textsuperscript{,228} the challenges in providing high-quality treatment to prevent and manage it\textsuperscript{,18} and the contributing nuances associated with prescribing medication to children and adolescents argue for a better method to appropriately identify patients at-risk for and currently with CINV in real-time and for secondary data use. Therefore, phenotyping methods may offer a mode to identify at-risk or symptomatic patients, a needed component to support guideline implementation, such as CDS\textsuperscript{.102,105,208} First, a comprehensive understanding of the data quality is necessary, and the data quality of CINV documentation has not yet been described. In response to this gap, the purpose of this study was to conduct a mixed-method study to describe the completeness, concordance, and heterogeneity of CINV documentation in an EHR system, and to develop a data-driven approach to improve identification of patients with CINV using clinical terminologies.

Materials and Methods

Phase 1: Documentation of CINV

Data source

A retrospective cohort study was conducted using data from the EHR of pediatric and young adult oncology patients at a large, urban hospital that includes a stand-alone children’s hospital, inpatient and outpatient cancer clinics all within an NCI-designated Comprehensive Cancer Center. This study was approved by the Institutional Review Board at Columbia University; a waiver of informed consent was granted because it was determined that the study involved no more than minimal risk to the subjects and could not practically be carried out without the waiver (IRB-AAAR9461).
Sample

Subjects 26 years of age or younger who received one of the drugs, or drug combinations, classified by published guidelines for children and adults as highly-emetogenic chemotherapy (HEC)\textsuperscript{175,176} were included in the analysis. This sample is a subset of the cohort, which included patients receiving both highly- and moderately-emetogenic chemotherapy and was described in detail in the previous study for this dissertation (Chapter Three, p.58).

Procedures

The EHR system was entered and the patient-specific medical record number for each patient who had received HEC in the cohort previously described in Chapter Three was inputted into the system. This allowed entry into the patient-level record, specifically the AllScripts application, which provides complete access to all clinical documentation. Multiple domains of the EHR were explored and documentation was abstracted from the follow-up encounter following administration of HEC.

The follow-up encounter was defined as the clinical encounter following the administration of highly-emetogenic chemotherapy, and the specific definition was determined by the location where the patient received HEC. For patients who received HEC in the inpatient setting, this was defined as the documented assessments during the acute phase of chemotherapy, up to 24-hours following completion of chemotherapy for the first chemotherapy cycle or through discharge from the hospital, whichever came first. All clinical documentation was assessed following the date of first administration of chemotherapy through the acute phase by the prescribers, defined in this study as physicians or nurse practitioners, and registered nurses (RN).
For patients who received HEC in the outpatient setting, the follow-up encounter was defined as the subsequent clinical encounter where they were seen at the hospital or clinic after receiving the first chemotherapy cycle with HEC. The location of this visit (outpatient vs. inpatient) was confirmed through EHR review. If the patient was admitted to the inpatient unit following outpatient receipt of HEC, the follow-up encounter was defined as the first inpatient encounter documented in the EHR.

All documentation by prescribers and RNs relating to CINV in the EHR for the first follow-up encounter was assessed. For prescribers, all notes during chemotherapy administration through the acute phase were assessed for documentation about nausea or vomiting, and the history of present illness section was directly abstracted from the chart into the dataset as free text. The RN documentation was similarly assessed for any documentation about CINV. Types of documentation that was abstracted included the chemotherapy administration notes, all symptom assessments, flowsheets, and nursing discharge summaries, educational, or miscellaneous notes. The number of documents assessed per patient was recorded.

From each follow-up encounter, documentation of CINV assessment by prescribers and/or RN was abstracted, and if documented, the documentation was assessed for the presence or absence of CINV. The symptom was coded as assessed if there was a specific comment about the presence or absence of nausea, vomiting, or similar terms. CINV was coded as present if there was any mention in text or discrete structured datapoint that acknowledged the presence of nausea, vomiting, retching, or if there was a documented emesis event on the RN flowsheet. If CINV was present, any text about the severity, temporality, or any other relevant descriptors of the symptom was also abstracted into the dataset. Administration of chemotherapy at the follow-up encounter was also abstracted from the medication administration record of the EHR. Finally,
three types of billing codes, specifically the ICD-10 codes, from the encounter were abstracted: primary oncologic diagnosis, encounter for or encounter following chemotherapy, and CINV-related codes. The EHR sections of interest are described in Appendix D. This list was informed by a pilot project conducted previously (abstract accepted, AMIA Symposium 2019).

**Outcome measures**

From each follow-up encounter, the following outcomes were described: the completeness of the EHR documentation defined as 1) if CINV was assessed in the documentation by prescriber; 2) if CINV was assessed in the documentation by RN; 3) if CINV was documented as present by prescriber; 4) if CINV was documented as present by RN; the concordance of the EHR defined as 1) if assessments by both the prescriber and the RN were available, were the two assessments in agreement; and 2) if the ICD-10 codes were in agreement with the data abstracted from the prescriber’s documentation within the EHR for a) primary oncologic diagnosis b) visit for chemotherapeutic encounter and c) presence of CINV symptoms; and the heterogeneity of the EHR documentation was defined as the number of notes and locations within the EHR that were assessed to identify the prior outcomes.

**Data Analysis**

Following data abstraction from the EHR, quantitative variables were coded as binary or categorical. For these variables, descriptive statistics were computed to provide with frequency tables. A bivariate analysis was then conducted using Chi-square to assess the association between the clinical and demographic variables and the outcomes of interest (i.e. CINV assessment, CINV present as reported by prescriber and RN, ICD-10 codes, and agreement by
provider type and ICD-10 codes). For associations from the bivariate analysis with a p-value < .05, simple logistic regression was conducted to further describe associations between predictors and outcomes; odds ratios were calculated. The proportion of patients for whom the assessment for CINV was concordant between prescriber and RN notes, as well between prescriber documentation and ICD-10 codes for oncologic diagnosis, visit for chemotherapy, and CINV were all calculated. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

**Phase 2: SNOMED-CT Overlay and Mapping through UMLS**

After the Phase I study was conducted from the patient-EHR, the UMLS Metathesaurus Browser,\textsuperscript{221} which includes SNOMED-CT, \textsuperscript{50} was explored to identify the related terms and concepts for CINV. Both browsers were utilized because SNOMED-CT is a commonly-used terminology for processing healthcare data (e.g. billing, phenotyping); and UMLS provides a link with other terminologies that may be necessary to comprehensively phenotype CINV. In the SNOMED-CT web browser, the string “Chemotherapy-induced nausea vomiting” and segments of this string were entered to identify any related terms. The pre-coordinated concept was then explored in UMLS Metathesaurus to identify other related terminologies for the concept. All concept unique identifiers (CUI), lexical or term unique identifiers (LUI), and atom unique identifiers (AUI), listed in UMLS and classified under nausea, vomiting, or chemotherapy-induced nausea (and/or) vomiting were identified. The ICD-10 diagnosis codes abstracted during Phase I, specifically for primary oncologic diagnosis, antineoplastic encounter, and follow-up from antineoplastic encounter were also included in our mapping. UMLS was also referenced to identify codes for specific chemotherapy drugs through RxNorm, which links to many drug vocabularies commonly used in pharmacy management.\textsuperscript{223}
Qualifiers and modifiers were also included in the mapping process; these were identified both through the UMLS search as well as the clinical documentation abstracted in Phase I and were categorized as post-coordination expressions. The Interactive MetaMap, a freely-available indexing tool that has natural language processing capabilities, was explored to determine the utility of natural language processing specifically to determine negation of symptoms. Finally, two validated instruments for CINV assessment, the pediatric nausea assessment scale (PeNAT) for pediatric assessment and the MASCC Antiemesis Tool (MAT) for adult assessment were utilized to ensure all terms relevant to CINV assessment were included in our concept mapping. In an iterative process, a diagram of all related terms and concepts of CINV mapped through UMLS that would reflect complete assessment and documentation of CINV was developed.

After fully mapping the concept, each patient-level encounter with a documented CINV assessment was analyzed to determine if the concept mapping would identify the patient as either having or not having CINV and, if available, the qualifiers and modifiers to describe the severity and temporality of CINV. Each documented assessment of CINV was classified as follows: 1) able to determine CINV status with a pre-coordinated expression available in the documentation, 2) able to determine CINV status using the post-coordinated expression or 3) able to partially determine CINV status using the post-coordinated expression. For assessments where the presence or absence of CINV was documented, but another domain (e.g. temporality, severity), was not, these would be counted as partially identified using a post-coordinated expression. The frequency of pre- and post-coordination expressions to identify both the prescriber and RN documented assessments were described. Two researchers (MB and MA) independently coded
20% of all cases to ensure reliability, and any disagreements were resolved through discussion and if necessary, through a third-reviewer.

Results

Phase 1

**EHR assessment of CINV.**

The inclusion criteria yielded 127 subjects in the retrospective cohort receiving highly-emetogenic chemotherapy over a 3-year period. The characteristics of the sample are described in Table 4.1. One patient did not follow-up with a prescriber, and therefore only had RN documentation available. In addition, all except for one patient who was admitted following outpatient receipt of HEC, were in the same location as the HEC administration.

| Table 4.1: Summary of Sample Characteristics (n=127) |
|-----------------|-----------------|
| **Sex**         |                 |
| Male            | 68 (53.5%)      |
| Female          | 59 (46.5%)      |
| **Insurance (primary)** |       |
| Commercial      | 52 (40.9%)      |
| Non-commercial  | 75 (59.1%)      |
| **Age group**   |                 |
| 0 – 5M          | 5 (3.9%)        |
| 6M – 11Y        | 51 (40.2%)      |
| 12Y – 17Y       | 27 (21.3%)      |
| 18Y < 26Y       | 44 (34.7%)      |
Table 4.1: Summary of Sample Characteristics (n=127) (cont.)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>80 (63%)</td>
</tr>
<tr>
<td>Not White</td>
<td>47 (37%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>85 (66.9%)</td>
</tr>
<tr>
<td>Hispanic or other</td>
<td>42 (33.1%)</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>92 (72.4%)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>35 (27.6%)</td>
</tr>
<tr>
<td><strong>Provider location</strong></td>
<td></td>
</tr>
<tr>
<td>Pediatric</td>
<td>98 (77.2%)</td>
</tr>
<tr>
<td>Adult</td>
<td>29 (22.8%)</td>
</tr>
<tr>
<td><strong>Chemo type</strong></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>34 (26.8%)</td>
</tr>
<tr>
<td>Non-cisplatin</td>
<td>93 (73.2%)</td>
</tr>
<tr>
<td><strong>Cancer type</strong></td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>62 (48.8%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>38 (29.9%)</td>
</tr>
<tr>
<td>CNS</td>
<td>15 (11.8%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12 (9.5%)</td>
</tr>
<tr>
<td><strong>Cancer status</strong></td>
<td></td>
</tr>
<tr>
<td>First occurrence</td>
<td>115 (90.6%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>12 (9.4%)</td>
</tr>
</tbody>
</table>
Completeness of documentation.

Prescriber assessment of CINV was documented in the EHR for 95 patients (75.4%). Factors associated with an increased likelihood of documenting CINV assessment included chemotherapy regimen and sex. Receiving a cisplatin-based therapy as the HEC regimen was significantly associated with having CINV assessment documented in the EHR (OR: 4.3, CI95: 1.2 – 15.3). Male sex was also significantly associated with a lower odds of having CINV assessment documented compared with female sex (OR: 0.37, CI95: 0.15 - 0.88). Of 95 patients where an assessment was documented, CINV was present in 63 (66%); none of the predictors were found to be significantly associated with a documented presence of CINV.

Of the 127 patients who had follow-up encounters with the RN, nursing assessment of CINV was documented in 72 patients (57%). Patient location during the follow-up encounter was significantly associated with RN documented assessment with those seen in the inpatient setting less likely to have a documented CINV assessment (OR: 0.04, CI95: 0.01 - 0.32). Of the 72 patients for whom assessment was documented, 40 (56%) reported CINV as present; none of the patient- or encounter-specific variables were significantly associated with the documented presence of CINV. Twenty-five (63%) of those where CINV was documented was present were from inpatient structured flowsheets reporting the number of emesis episode(s); in these documented assessments, no further descriptors about the symptom were available in the documentation.

Concordance of documentation.

Fifty-nine (46%) of all patients had a CINV assessment documented by both prescriber and RN; of these, 40 (68%) reported concordant assessments. Reasons for discordance varied but included recent report of CINV by prescriber and an assessment of no symptoms by RN marked
in a discrete structured checklist. Another type of discordance was due to an emesis episode documented by the RN with the prescriber reporting no symptoms. Table 4.2 provides examples of concordant and discordant assessments. Of the 40 concordant assessments, 32 (80%) agreed that CINV was present, and the remaining eight agreed that CINV was not present (Figure 4.1).

Table 4.2: Examples of Discordant Documentation

<table>
<thead>
<tr>
<th>Prescriber documentation</th>
<th>RN documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No acute events overnight. Afebrile, no cough or runny nose. No problems with constipation or diarrhea. No nausea/vomiting. Tolerating chemotherapy well so far. Appetite ok. No bleeding. No pain.</td>
<td>Patient vomited immediately after first attempt of prednisone dosing at 1700. Second dose of prednisone attempted at 1800 with medication crushed in ice cream. Patient did not tolerate and vomited. Mother present at bedside.</td>
</tr>
<tr>
<td>No significant events overnight. Afebrile. No vomiting or diarrhea. Constipation - no BM since Tuesday. Appetite has been good. No cough, runny nose, or other URI Sx's. No reports of hematuria. No other bleeding signs or Sx's reported. No problems with pain. No other problems or concerns reported</td>
<td>*NO TEXT, CHECKED 1 EPISODE EMESIS</td>
</tr>
<tr>
<td>Started chemo 3/21, w/delayed vomiting yest and today. Seemed to have jaw pain, but teething. Seems fussy changing position. Remains afob.</td>
<td>*NO TEXT, CHECKED NO SYMPTOMS</td>
</tr>
<tr>
<td>C/o nausea, but no vomiting. Is still eating and drinking.</td>
<td>Nausea: None and Zofran given ATC at home. Vomiting: None.</td>
</tr>
</tbody>
</table>

Of the 126 patients who had follow-up encounters with a prescriber, twenty (15.9%) included an ICD-10 code for CINV compared to the 61 reported in the EHR documentation. Of the 95 patients where CINV was assessed by the prescriber, 47 (49.5%) of the documented assessments agreed with the ICD-10 code for that encounter. Of the 20 patients where the ICD-10 code for CINV was present, 17 (85%) of these agreed with the provider assessment. ICD-10 codes for chemotherapy encounters were correctly documented in 81 patients (63.8%), whereas
ICD-10 codes for primary oncologic diagnosis were correctly documented in 100% of the patients.

**Heterogeneity of documentation.**

In total, 390 prescriber notes and 480 RN notes were reviewed. Prescriber documentation was primarily abstracted from the oncology prescriber note(s) during the acute phase of chemotherapy (up to 24-hours following completion of all chemotherapy). However, this class of notes included six distinctly-named documents depending on provider setting (adult, pediatric oncology) and location (inpatient, outpatient). The HPI, an unstructured data domain, was the primary source for documentation abstraction.
Nursing documentation was abstracted from six unique locations including flowsheets, shift assessments, and various nursing-specific notes. The flowsheets and shift assessments were all structured data capture, with an option to include free-text; the nursing notes were a combination of structured and unstructured data. The locations, note titles, and EHR domains are provided in Appendix D.

**Phase 2**

**Concept mapping of CINV.**

Through an iterative approach, the concept map for the components of CINV documentation that would be needed to evaluate data quality and to accurately and completely identify patients with CINV from EHR data using a data-driven approach was developed. First, in the SNOMED-CT browser, the concept “chemotherapy-induced nausea and vomiting” was entered and identified a pre-coordinated expression, concept ID 18846006 (Figure 4.2). The diagram for this concept provided additional information, specifically that nausea and vomiting “is a disorder” that is “associated with chemotherapy” and the “finding site is upper gastrointestinal tract structure.” The parent term did not have any related children.

![Figure 4.2: SNOMED-CT Concept Diagram for CINV](image)
Each related concept ID from SNOMED-CT was entered into the UMLS Metathesaurus Browser using the “term search” and identified the SNOMED concept, C0401160, semantically categorized as a “Pathologic Function, T046”. Within this concept, 10 associated atom unique identifiers were identified, most of which were from either the SNOMED-CT terminology and the Consumer Health Vocabulary, a terminology designed to complement the medical terminologies to aid the needs of the consumer. These terms, or atoms, were reviewed and were consistent with the CINV-related terms identified during Phase I of this study. Twenty-nine related contexts were also identified, 13 of which were within the SNOMED-CT terminology and determined to be most relevant (other contexts included non-English language use of the concept, and “sibling” contexts such as travel-related nausea vomiting which we determined to be outside the scope of our investigation). Of these 13 contexts, all were located under “clinical finding.” This means that information about CINV would most likely be found in clinical documentation, such as those examined during Phase I. With this information, the first iteration of the concept mapping was developed which identifies the presence or absence of CINV.

Our next iteration started with a review of the text found in the EHR documentation and the two validated CINV assessment tools to identify any outstanding information that was needed to completely describe CINV. The main findings from this iteration revealed the need for qualifiers and modifiers to convey the temporality, frequency, and severity or bother of the symptom. These domains sometimes were found in the EHR documentation when CINV was documented as present, however they were more clearly found in the validated instruments. To capture temporality, multiple concepts were identified, however “time of onset” (C0449244), was determined to be most accurate. In addition, clarification about the timing in cases where the symptom was previously present but now resolved was also important (e.g. “nausea and
vomiting after last cycle, now resolved”). The concepts for “Present” (C0150312) and “Absent” (C0332197) were also included in the mapping. After mapping temporality, frequency was explored and “Symptom frequency” (C0436350) was identified as the most related term. Finally, severity was explored. Although the documentation infrequently captured this characteristic, the CINV assessment tools, specifically related to nausea, ask about how bothersome or severe the symptom is for the subject. For vomiting, this may also be captured by frequency. To assess severity, SNOMED-CT has a specific concept “Nausea and vomiting status” (C1319170) with symptom “Nausea and vomiting severity.” Because this is very specific, two severity modifiers, “Moderate” (C0205081) and “Severe” (C0205082) were included.

At this iteration, the full concept of CINV was mapped; however, identifying these patients prospectively was unlikely to be successful using this framework. Therefore, additional diagnostic and medication terms were explored: first, ICD-10 codes for primary oncologic diagnosis (C00-C97; C0006826), “Encounter due to Chemotherapy session for neoplasm” (C0476658) and/or “Follow-up examination after chemotherapy for malignant neoplasm” (C0476668); and second, RxNorm because this terminology can be used to identify patients receiving certain drugs in the EHR, such as highly-emetogenic chemotherapy drugs. The ICD-10 code for CINV was not included given its poor sensitivity and specificity in Phase I. Figure 4.3 outlines the final concept mapping of CINV.
Figure 4.3: Concept Mapping of CINV

- SNOMED-CT: ‘chemotherapy induced nausea and vomiting’
- Disorder
- Associated with chemotherapy
- Finding site: Upper GI tract

Map through UMLS
- Pre-coordinated expression available
- 8 Synonyms
- 32 Relations
- 10 Atom unique identifiers
- 29 Contexts
- Presence or absence
- Temporality
- Frequency
- Severity

Need for Qualifiers/Modifiers

Need for Diagnostic Codes
- ICD-10
  - Cancer
  - Encounter for chemotherapy
  - Follow-up following chemotherapy
  - ReAssm
  - Chemotherapy
  - Anti-emetics

Next Steps
- Validation testing
- Develop algorithm
- Workflow considerations
Finally, although MetaMap was able to identify the concept of CINV from the text if it was a positive assessment (“patient complaining of nausea and vomiting”), it did not capture negation in any of the patient examples. The “NegEx” option theoretically should enable the algorithm to identify negative concepts. This was not true in this setting. In addition, the nursing symptom assessments were often discrete, structured documentation (e.g. Nausea √; or Emesis = 1). If the nurse did not explicitly write one of the atoms associated with CINV in the free text section, it would not identify the concept as “nausea” or “vomiting.” Therefore, MetaMap and natural language processing methods were not included in the mapping.

**Assessing the data quality of EHR documentation utilizing CINV concept map**

Of the 95 patients who had a prescriber assessment of CINV documented, a related term from the concept map was identified in the EHR documentation. For 25 patients (26%), a precoordinated concept for CINV status was documented in the EHR. Most (n=16, 64%) of these patients had a negative prescriber assessment of CINV. Applying the post-coordinated expression to the patient documentation allowed us to identify the status of six patients (6%). In the 72 patients (76%), applying the post-coordinated expression was partially successful in identifying the CINV status. This means that some component of CINV was captured. In fact, in most patients (n=55, 76%), post-coordinated approach identified two or less domains of CINV assessment. Severity, noted through terms such as “severe nausea” or “mild nausea and vomiting,” was the most commonly-missing CINV domain and only available in nine (9%) to apply the post-coordination approach.

Of the 72 patients who had a RN assessment of CINV documented, 28 (37.8%) had a clear precoordinated expression available in the documentation. Only one of the 28 assessments were positive for CINV. Applying the post-coordinated expression was partially successful in the
remaining 45 patients CINV status; this approach identified either the presence/absence of the symptom but did not provide severity or temporality. Most of the RN documentation of CINV was through structured data capture that did not capture the modifiers and qualifiers, specifically severity and temporality.

**Discussion**

This mixed-methods study describes the documentation of CINV assessment in the EHR and developed a path to improve the complete and concordant capture of CINV using available terminologies. The results of Phase 1 demonstrate that documentation in the EHR of CINV is frequently incomplete and varies by provider type; 75% of prescribers and 58% of RNs documented an assessment in a cohort of children, adolescents, and young adults receiving HEC. Also, when CINV assessment was documented, the rate of concordance by provider type was 72%. Phase 2 of this study utilized both the EHR documentation and validated instruments to assess CINV, and the researcher found that the EHR structure is suboptimal and does not currently support the relevant terms and concepts needed to accurately and completely describe the symptom.

CINV should always be assessed, particularly when a patient is receiving HEC. An ongoing challenge with EHR documentation is incomplete data, and one cannot assume that data that is not present is the same as a negative outcome. Missing data is generally attributed to a mistake or more commonly, an assumption of pertinent negative findings; however, the researcher purposefully chose a cohort of patients receiving HEC and the highest risk CINV. The proportion of missing data in this cohort, in contrast to the known prevalence of CINV, suggests that other factors may be at least partly responsible. Consideration of incomplete
documentation includes workflow challenges, and it is likely that CINV was assessed by many of the clinicians; however it was not documented.

In cases where the EHR demonstrated the presence of CINV, the incompleteness of documentation was notable. Few assessments fully expounded on the temporality, severity, and frequency of the symptom, although validated assessments include these components and guideline recommendations vary depending on them. The incompleteness noted in this study may be related to lack of a validated assessment tool capturing the data and integrated into the EHR in addition to workflow challenges. Complete documentation of CINV symptoms by clinicians may not be feasible to implement and sustain in a busy clinical workflow. The concept mapping, developed both from text in the EHR and from validated instruments, provides a pathway toward integration of patient-reported outcome measures into the assessment and documentation workflow. The effect of this integration is not well-studied; however, these findings support its potential utility to completely capture symptoms. Ultimately, incorporating and studying the utility of patient-reported outcome measures into the EHR is important. Although providers assess symptoms during clinic or inpatient visits, complete symptomatology is not well-captured in this EHR system.

Interestingly, two potential predictors for CINV documentation emerged with prescribers significantly more likely to document CINV assessment on females (p=.03) and patients receiving cisplatin-based regimens (p=.02). These are important findings given that historically, female sex has been considered a risk factor for nausea and vomiting in general, but also specifically for CINV, and cisplatin is one of the oldest chemotherapies that was known to cause CINV. A recent study developing a prediction tool to identify at-risk adult cancer patients for CINV, however, did not find that sex was a significant predictor of CINV.
Similarly, although cisplatin has historically been the gold-standard for studying CINV pathophysiology and pharmacologic interventions, all chemotherapy classified as HEC have a >90% likelihood of causing CINV within 24 hours of administration if not otherwise treated. Therefore, both associations suggest that, as often acknowledged in data quality, there are biases that exist relating to EHR documentation. Bias to assess certain patients for CINV supports the importance of systematic symptom screening in high-risk patients regardless of non-validated patient factors and initiatives to increase awareness by clinicians about the importance of documenting clinical assessments.

Applying the post-coordinated expression that was developed during concept mapping correctly identified the presence or absence of $\geq 85\%$ of the patients who had a documented assessment of CINV by prescriber and 100% of those with RN documentation. The majority of these were partial assessments, which is related to incomplete data, specifically about the severity and temporality of the symptom. This is also important because available terminologies do not support complete documentation of cancer-related symptoms and required post-coordinated efforts. Further expansion of existing terminologies should include focus on cancer-related symptoms.

Although using a post-coordination approach did not completely describe CINV symptoms, the ability to identify the presence or absence of symptoms is important. Similar to other studies using post-coordinated approaches to phenotype patient-level data, our study suggests that this may a feasible approach to leverage the already-existing EHR data for decision-support systems, billing purposes, and retrospective data capture. This study provides the first step toward identifying patients at risk for CINV simply by utilizing the ICD-10 and RxNorm terminologies, and to identify patients with CINV using the full UMLS mapping
and post-coordinated approach. The ability to identify “at-risk” and “diseased” patients are both important to phenotype patients and develop interventions, such as CDS. These systems can then provide decision support for early identification of patients who should receive prevention of or treatment for CINV. CDS may be an effective guideline implementation tool, especially when it is integrated into the workflow, such as through EHR integration or supported by patient-reported data.

This study provides the foundational knowledge for EHR documentation to completely and accurately describe a cancer-related symptom. This study, however, was conducted manually and has not been automated into a programmable algorithm. The researcher chose this approach to increase the granularity and improve the internal validity of the findings; however, similar to historical phenotyping, the manual approach will not be sustainable across multiple settings and automated development will be needed to move toward predictive modelling and CDS development.

**Strengths and Limitations**

This study has some notable strengths and limitations. To our knowledge this is the first mixed-method study examining the data quality, specifically the completeness, concordance, and heterogeneity of CINV assessment and documentation. Our approach includes both knowledge engineering by leveraging existing data and terminology structures, and bottom-up learning from new data in the EHR. This comprehensive and innovative methodology to analyze a common cancer symptom contributes new knowledge to the field and can inform the next generation of EHR systems.

It is important to acknowledge the limited generalizability of this study due to using data from a single-institution and a single EHR system. The findings, specifically the completeness
assessment, may vary widely by hospital or clinical setting as well as by EHR system. Future studies should examine differences across institutions and/or EHR systems to test the validity of this approach in multiple settings. Because CINV is a universal cancer symptom, however, the researcher anticipates that the concept mapping will largely be generalizable across sites that utilize EHR systems.

Another limitation of this study is the focus on three domains of data quality: completeness, concordance, and heterogeneity. There are other domains of data quality that are associated with challenges utilizing EHR data for secondary use, such as correctness, plausibility, and currency of data.\(^{210}\) However, for the first two domains, correctness and plausibility, without another validation source, such as paper charts or patient-reported measures for comparison, cannot be fully described. To assess currency of data, the timing of data entry or data logs are often reviewed, and access to EHR audit records was not feasible to obtain for this study. We did, however, include three dimensions to strengthen our assessment of the data quality of CINV documentation in the EHR.

**Conclusion**

In summary, this study is a mixed-method, two-phase study that characterizes the data quality of CINV assessment in the EHR to develop a comprehensive data-driven approach to capture this symptom in the next generation of EHRs. The findings highlight the gaps in capturing symptoms in modern terminologies such as SNOMED-CT, a weakness that should be studied further to move toward phenotyping and predictive modelling of cancer symptoms. Notably, this study highlights the importance of incorporating patient-reported information into the EHR to improve completeness and concordance of symptom documentation, both in real-
time for future decision support systems, as well as in population-based studies to understand and measure cancer symptoms across multiple settings.
Chapter Five: Discussion and Conclusion

The goal of this dissertation is to provide a better understanding of clinician decision making for cancer patients. This dissertation is comprised of Chapter One, an introduction and review of the literature for relevant topics to this dissertation; Chapter Two, a systematic review describing clinical decision support (CDS) systems that have been used in clinical cancer settings to guide therapeutic decision making and the effect of CDS on care delivery process and patient outcomes; Chapter Three, a quantitative study describing the rate of guideline concordant care (GCC) provided for management of chemotherapy-induced nausea and vomiting (CINV) and identifying predictors of receiving GCC; and Chapter Four, a mixed-methods study evaluating the completeness, concordance, and heterogeneity of clinician documentation of CINV. Chapter Five is comprised of key findings of each study, the strengths and limitations, clinical and research implications, and future research.

Summary of Results and Key Findings

Chapter Two

Chapter Two describes the first study of the dissertation. The research question in this study was “What clinical decision support systems been tested in cancer settings to guide therapeutic decision making and in what ways were they successful?” Through a systematic review of the literature guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, ten studies were identified that met the predetermined inclusion criteria. The study design varied, and the most common was pre-post interventional design (n=5). Seven studies were conducted in Europe; the remaining (n=3) in the United States. Of the ten studies, three used cancer treatment focused CDS interventions, and all studies
focused on breast cancer management. The remaining seven studies focused on symptom or supportive care management; the most common symptom studied was pain (n=3). Of the seven symptom or supportive care CDS studies, six incorporated patient-reported symptom information into the algorithm to inform the CDS recommendation to the clinician. Three of the ten studies used CDS systems that were integrated into the electronic health record (EHR) system, and all studies reported the CDS recommendations were informed by a published guideline.

The outcomes measured also varied, and although all studies measured process outcome measures and/or patient outcomes, the measures utilized were not consistent. The most common process measure was adherence to the CDS recommendation, and the most common patient outcome measure was patient-reported pain. Through qualitative synthesis of the study results, we identified a trend in the ten included studies toward both provider- and patient-benefit from utilization of CDS. Of the nine studies that measured process outcome measures, five demonstrated a significant increase in utilizing the CDS recommendation. This was most commonly measured by clinician adherence to the CDS recommendation. Of the six studies that measured patient outcomes, four demonstrated significant improvement in patient outcomes; most of these were through patient-reported outcome measures (PROMs).

Although there was variability in study design, CDS intervention, and outcome measures, this systematic review indicates that although CDS are a national focus to improve the quality of care, reduce errors, and increase shared decision making, the use of CDS in cancer therapeutic decision making has not been widely studied or published. Three of the ten studies were integrated into the electronic health record system, a known facilitator to guideline implementation. Also, five of the six studies incorporated PROMs into the CDS, and three of these found a significant benefit to either process and/or patient outcomes. Integration of PROMs
into clinical care, specifically through CDS integration, has been cited as a strategy to improve
guideline implementation both broadly but also in cancer care delivery.\textsuperscript{115,130}

Chapter Three

Chapter Three describes the second study of this dissertation. The research question in
this study is, “What proportion of patients receiving emetogenic chemotherapy also receive
guideline concordant care for the prevention of acute CINV?” To answer this question, we
conducted a retrospective cohort study from 2016 – 2018 at a single institution and identified
patients less than age 26 years who were receiving emetogenic chemotherapy. Of the 180
patients identified, 36\% of patients received guideline concordant care prior to the administration
of chemotherapy. These findings were further explored through bivariate and multivariable
analysis, which found provider specialty, patient sociodemographic factors, and clinical factors
(cancer type, chemotherapy regimen) were associated with receiving GCC.

Patients who received care in pediatric oncology were significantly less likely to receive
GCC compared to those treated in adult oncology (p<.0001). This finding may be due lack of
knowledge about the guideline but also may be due to concerns about prescribing certain classes
of drugs to children that may interact with chemotherapy. For example, the 2013 guideline for
prevention of acute CINV in children with cancer, used to define GCC in this study,
recommended the use of NK1RAs for patients age 12 and older due to limited data in children.
In this study, of the 71 patients age 12 – 18 years, only 26\% received the recommended NK1RA.
Interestingly, a 2017 update of the guideline recommends using NK1RA for children over 6-
months of age, and only 10\% of patients age 6-months to 12 years in this study received an
NK1RA, suggesting protracted guideline implementation, widely recognized in the literature.\textsuperscript{74}
In addition to the slow dissemination of knowledge, discomfort prescribing this class of
medications may also be a barrier. Although an important class of drugs for CINV control, NK1RAs specifically have the potential to interact with other commonly-prescribed chemotherapy drugs, including ifosfamide, anthracyclines, and cyclophosphamide.196

Another barrier to prescribing GCC in children is concern about concomitant medications related to their prescribed treatment, specifically dexamethasone.18 Because additional corticosteroids may be contraindicated in acute lymphoblastic leukemia and central nervous system tumors, the two most common types of childhood cancer, optimizing antiemetics is challenging in these patients. In contrast, the most common cancers in adults are solid tumors, and the same barriers to dexamethasone use do not exist.192 In a sub-group analysis only of patients with solid tumors, however, only 62% received dexamethasone. In addition, the alternative guideline recommended medications for when the primary recommended medications are not appropriate are known to have significant adverse effects and therefore may not commonly be used, and only 35% of patients in our study received additional anti-emetics. This may lead to undertreatment of CINV and potentially worse symptom management for children with cancer.

Insurance status was also identified as a factor associated with receiving GCC, and patients who had commercial insurance were more likely to receive GCC (p=.02). This finding highlights potential disparities in prescribing that have been reported in adult breast cancer patients.66 In addition, a prior study in children with acute myeloid leukemia found a significant association of antiemetic rescue, prescribing an adjunct therapy for treatment of CINV, and insurance status; children with private insurance were significantly less likely to require rescue medication.48 Chapter Three in this dissertation supports this association, and insurance status may support a disparity in how CINV is assessed and/or managed.
Finally, type of chemotherapy regimen was identified as a factor related to receiving GCC, with patients receiving cisplatin-based regimens more likely to receive GCC \((p=.01)\). This finding may be related to the historical knowledge of clinicians who recall that early studies testing antiemetics were conducted mostly in patients receiving cisplatin.\(^{188,244}\) This highlights another important area for future implementation and dissemination efforts. To optimize CINV prevention and management, providers should be aware of the emetogenicity classifications that are used to develop specific guideline recommendations, but an automated approach that prompts the guideline-based recommended anti-emetic regimen may also increase adherence to guidelines. Strategies to improve guideline awareness should include education, preferably interactive, audit-and-feedback, and clinical decision support integrated into the EHR.\(^{76}\) In summary, this second study reports a low-rate of guideline concordant care delivery for children, adolescents, and young adults receiving emetogenic chemotherapy and identifies factors to focus on for future improvement.

**Chapter Four**

Chapter Four describes the third study of this dissertation. In this study, the research question is “What is the status of documentation of CINV in the EHR specifically related to the completeness, concordance, and heterogeneity of the documentation?” EHR integration is an integral component of guideline implementation strategies such as CDS systems, and this study is a first step toward data-driven phenotyping methods used to identify patients with common diseases.\(^{216,217}\) To define a phenotype through a data-driven approach utilizing EHR data, the data quality of the available documentation or clinical characteristics must first be evaluated. To our knowledge, the data quality related to cancer symptoms, such as CINV, has not been
described, and phenotyping methods to identify patients at risk for CINV or experiencing CINV have not been developed.

The purpose of this study was therefore to conduct a mixed-methods study to examine the completeness, concordance, and heterogeneity of the documentation in the EHR of 127 children, adolescents, and young adults receiving highly-emetogenic chemotherapy. The results showed that, although most clinicians documented an assessment acknowledging the presence or absence of CINV (75% for prescribers; 58% for RNs), a complete assessment of CINV was not documented in many patients. Specifically, the symptom’s severity and temporality were usually not documented. Regarding the concordance of documentation, of patients where both a prescriber and RN documented an assessment of CINV (n=60), 72% were concordant. When comparing the ICD-10 billing codes with the prescriber documentation, of the 95 patients where a prescriber assessed CINV, 50% of the ICD-10 codes were concordant. Of the 20 patients where an ICD-10 code for CINV was present, 85% were in agreement with the prescriber documentation. In contrast, the ICD-10 codes for primary cancer diagnosis were correct in 100% of patients.

By mapping the concept of CINV through the United Medical Language System and utilizing our findings from the EHR documentation as well as validated measures to assess CINV, we developed a post-coordination approach that would identify the presence or absence of CINV in 85% of prescriber documentation and 100% of RN documentation. This approach, however, did not fully capture the granularity of CINV status related to the severity and temporality. Integrating patient-reported outcome measures into the EHR is a potential strategy to increase the completeness of the documentation of CINV. This study contributes new knowledge to the field of phenotyping cancer-related symptoms and provides a framework for a
CDS system to improve adherence to CINV guidelines for pediatric, adolescent, and young adult patients with cancer.

**Strengths and Limitations**

This dissertation has some strengths and limitations. A major strength of the dissertation is that it provides a comprehensive assessment of CINV management in children, adolescent, and young adults with cancer and includes possible methods to address the low adherence to GCC. We identified a low rate of GCC in this understudied population, evaluated CDS interventions previously utilized for cancer management, and then assessed the current documentation of CINV in the EHR. The results of this dissertation support that incorporating CDS infrastructure into the EHR to improve CINV assessment and management may be feasible.

Another strength of this study is the level of granularity that was leveraged in Studies Two and Three. In Study Two, patient-level data strengthened the internal validity of the findings because the prescribing and administration of anti-emetics could be confirmed through the EHR. Studies that utilize larger datasets, such as through insurance claims, are generally not able to provide this level of detail. In addition, Study Two compared anti-emetic prescribing and administration by two distinct provider specialties (i.e. pediatric oncology, adult oncology), and the patient-level data that was utilized to describe these characteristics further strengthens this study. The clinical practice or setting where a patient receives treatment may be difficult to accurately describe from a larger dataset.

Similarly, the ability to assess the heterogeneity of the EHR documentation through direct EHR navigation, and the completeness and concordance of the EHR documentation through abstracting multiple clinical notes, structured data, and billing codes is a major strength of Study Three. The granularity that could be assessed through patient-level records in the EHR
provided a more complete understanding of the data. These data are not routinely available through large datasets.

An important limitation of this dissertation is the limited generalizability. In Study Three, the documentation patterns and locations of documentation may vary by EHR system. Future studies should include assessment of the data quality to determine if the concept mapping and post-coordinated expression are useful across EHR systems. The use of standardized terminologies and mapping through UMLS should be generalizable across EHR systems, however, because the symptom definitions and patient-characteristics are universal to CINV.

Similarly, because this dissertation utilized data from a single institution, these results may not be generalizable across multiple settings, specifically the independent variables that were significantly associated with receiving GCC. The institution is a large hospital system, NCI-designated Comprehensive Cancer Center, and a Minority-Underserved NCI-Community Oncology Research Program. It provides care to a diverse population that includes a significant proportion of children, adolescents, and young adults in the metropolitan New York City area with cancer. Future studies should explore risk factors for CINV in non-urban, rural, and community oncology practices to determine external validity of the identified associations with receiving GCC.

Another limitation of this study is that we focused on one cancer symptom, CINV, to further explore decision making processes and documentation in cancer care delivery. This symptom was chosen because there are effective strategies to prevent and manage CINV and it is one of the most commonly-reported symptoms that affects quality of life and may reduce adherence to treatment regimens. The findings may not be generalizable to other cancer
symptoms. We hypothesize that at least in part, these methods and findings can support future work in other common cancer symptoms, such as fatigue, pain, and mucositis.

**Implications and Future Research**

The implications of this dissertation research include both clinical and policy considerations, and these should be used to inform future work in guideline implementation using informatics-based approaches in pediatric, adolescent and young adult cancers.

**Research Implications**

First, CDS may be a beneficial intervention to guide decision making and improve knowledge translation from evidence base into pediatric, adolescent and young adult cancer clinical care, specifically for CINV prevention and management. Although CDS interventions have not yet been conducted and published in pediatric settings, tools have been developed and validated and are ready for future implementation studies. For example, the Supportive care Assessment, Prioritization and Recommendations for Kids (SPARK) is a web-based tool to facilitate symptom screening in children and adolescents with cancer with the capability to provide both provider- and patient-friendly feedback from guideline recommendations.\textsuperscript{245,246} These studies demonstrate that this tool is feasible and usable from a patient-perspective as a symptom screening tool for children ages 8 – 18 years of age. Although this symptom screening tool has not been tested as a CDS for clinicians, this work is promising and suggests that CDS systems will continue to be developed and tested for children and adolescent cancer symptom management. Symptom screening in general and specific symptom screening can be linked to CDS, similar to the studies identified in our systematic review.\textsuperscript{153-157,247} Importantly, none of these CDS interventions were developed for or tested in children or adolescents.
Another opportunity for future research is to intervene on the system rather than the provider or patient. The findings from Study Two identified provider specialty as a significant predictor of receiving GCC, and future studies should explore the feasibility of modifying the order entry system to automatically default to the guideline-recommendations for anti-emetic depending on emetogenic classification of the regimen. Study Three provides the building blocks needed to identify patients at risk for CINV, including ICD-10 diagnostic codes and RxNorm medication codes. By setting the default for a computerized provider order entry system to the appropriate antiemetic regimen, this may alleviate the workflow concerns that may be associated with a true CDS intervention. One example of a study that intervened at the system-level includes S1415CD, Trial Assessing CSF Prescribing Effectiveness and Risk (TrACER) (NCT02728596) through the NCI’s Cancer Care Delivery network. This cluster-randomized study is currently accruing patients and randomizes to usual care or an EHR modification to prescribe a medication to patients who meet guideline criteria by default. A similar study may be an appropriate strategy to improve guideline adherence for CINV prevention.

**Clinical Implications**

Another implication of this dissertation is the clinical impact of the low rate of GCC and specific multi-level factors associated with receiving GCC for prevention of acute CINV. Provision of GCC reduces CINV symptoms, therefore it is likely that the low rate of GCC may correlate to increased symptom burden and lower quality of life for children with cancer. This finding highlights the importance of supporting provider education and implementation strategies for CINV guidelines. The findings from this dissertation align with ongoing initiatives through the Children’s Oncology Group (NCT02847130) and across the NCTN network (NCT03204916) to identify and address barriers to guideline implementation for children, adolescence and young
adults with cancer. In addition, the results of this dissertation provide new knowledge, and factors identified in this study that are associated with not receiving GCC which should be validated and ultimately, used to inform future implementation interventions, such as audit and feedback, or development of CDS tools.

**Policy Implications**

In addition to the clinical implications of low rates of GCC for CINV in children, adolescents, and young adults, the policy and regulatory implications of these studies are important. Pediatric cancer is relatively rare and makes up only 1% of cancer cases.\(^{248}\) However, children are diagnosed at an average age of 6 years, and with 80% expected to become long-term survivors, symptom management and reduction of morbidity is essential. Four percent of federal cancer research funding goes to pediatric cancer, and pharmaceutical companies fund very little drug development in pediatrics.\(^{249}\)

This has been due to financial and regulatory concerns.\(^{199,204}\) In general, profits from pediatric medications when few children require medications are generally low. In addition, conducting clinical trials in pediatric settings require additional regulatory and clinical considerations that may be perceived as barriers to pharmaceutical companies. New regulations, specifically the Best Pharmaceuticals for Children Act, aim to incentivize pharmaceutical companies to provide pediatric-specific data and apply for pediatric indications. In fact, an increase in pediatric-specific indications has been noted, with most of these being anti-tumor drugs. These initiatives should continue to provide funding for this important, vulnerable population to ensure that supportive care medications are also developed, tested and approved to reduce morbidity and improve long-term outcomes.
Further, because effective medications are readily available to prevent and manage CINV, further studies are needed to understand their use and safety in children and adolescents. Specifically, post-marketing studies should be supported and conducted to characterize the true risks of concomitant medications, such as those identified with NK1RAs and chemotherapy. Finally, because dexamethasone may not be allowed for children with the most common pediatric cancers, further studies should focus on developing the most effective combination of anti-emetics for this group of patients who, in practice, are precluded from receiving GCC.

**Informatics Implications**

Finally, an important implication to acknowledge is the potential for post-coordination expression to correctly identify at-risk and patients with CINV. By harnessing the findings from our systematic review that EHR integration is an integral component of guideline implementation strategies such as CDS systems, Study Three of this dissertation demonstrated that although documentation is heterogeneous, frequently incomplete and discordant by provider type, characteristics in the EHR are documented that can be utilized to classify the symptom, at least in part, through available terminologies and data-driven approaches. This study provides baseline data for further development of a phenotyping algorithm and validation testing across multiple EHR systems.

The importance of CDS tools to improve healthcare delivery is clearly stated by the recent National Academy of Medicine in “The Learning Health System Series: Optimizing Strategies for Clinical Decision Support.” The panel acknowledges the importance of EHR data to inform CDS and that commitment to interoperability and collaboration across multiple stakeholders will be necessary to move the field forward. Specifically, understanding and developing a set of standards, including data standards for EHR are an integral component. The
findings from Study Three provide a step toward developing data quality standards for cancer symptom documentation in the EHR.

Conclusion

In conclusion, this dissertation described three studies to better characterize clinician decision making in cancer care delivery. This work is timely and important due to national efforts to improve the implementation of evidence into clinical practice. The findings from this dissertation support ongoing initiatives to improve implementation of the evidence base into cancer care delivery for children, adolescents, and young adults with cancer and to inform future strategies and interventions to integrate and sustain evidence-based interventions into clinical care.
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codes, clinical notes, and medications from electronic health records provides superior
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for electronic health record based automated adverse event and medical error detection in
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232. SNOMED CT International Browser. Chemotherapy-induced nausea and vomiting. 


## Appendix A: Search Strategy for Systematic Review

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Terms</th>
<th>Initial publications retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embase</td>
<td>(&quot;clinical decision support&quot;:ab,ti OR 'clinical decision support'/exp/mj OR 'decision aid':ab,ti OR 'decision aid'/exp/mj OR 'clinical decision support system'/exp/mj OR 'expert system':ab,ti OR 'expert system'/exp/mj) AND (&quot;cancer&quot;:ab,ti OR 'neoplasm'/exp/mj) AND (&quot;automated&quot;:ab,ti OR 'electronic':ab,ti)</td>
<td>173</td>
</tr>
<tr>
<td>OVID Medline</td>
<td></td>
<td>253</td>
</tr>
<tr>
<td>IEEE</td>
<td>“clinical decision support” and “cancer”</td>
<td>218</td>
</tr>
</tbody>
</table>
Appendix B: Chemotherapeutic Agents Classified as Highly- or Moderately Emetogenic\textsuperscript{175,178}

<table>
<thead>
<tr>
<th>Emetogenicity</th>
<th>Chemotherapeutic Agent 1</th>
<th>AND Agent 2 (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Cisplatin</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Carboplatin*</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Dactinomycin*</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Procarbazine</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>Etoposide*</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>Etoposide*</td>
</tr>
<tr>
<td></td>
<td>Thiotepa ≥ 300mg/m2*</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Cytarabine 3g/m2/dose*</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide ≥ 1g/m2*</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Methotrexate ≥ 12g/m2</td>
<td>n/a</td>
</tr>
<tr>
<td>Moderate</td>
<td>Aldesleukin &gt;12 to 15 million U/m2</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Arsenic trioxide</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Azacitadine</td>
<td>n/a</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>Bendamustine</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Carmustine &lt;250mg/m2</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Clofarabine</td>
<td>Etoposide</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide &lt;1g/m2</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Etoposide (oral)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Idarubicin</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Imatinib (oral)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Intrathecal chemotherapy (MTX, HCT, Ara-C)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Lomustine</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Methotrexate 250mg/m2 − 12g/m2</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin &gt;75mg/m2</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>
Temozolomide (oral)  n/a
Vinorelbine (oral)  n/a

* Classified by the ASCO guideline for adults as moderately emetogenic
## Appendix C: Anti-emetics Included in Retrospective Cohort Study

<table>
<thead>
<tr>
<th>Antiemetic</th>
<th>Class of drug</th>
<th>Guideline-recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>5HT3-receptor antagonist</td>
<td>Yes</td>
</tr>
<tr>
<td>Granisetron</td>
<td>5HT3-receptor antagonist</td>
<td>Yes</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>5HT3-receptor antagonist</td>
<td>Yes</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>Neurokinin1-receptor antagonist</td>
<td>Yes, with exceptions</td>
</tr>
<tr>
<td>Fosaprepitant</td>
<td>Neurokinin1-receptor antagonist</td>
<td>Yes, with exceptions</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Corticosteroid</td>
<td>Yes, with exceptions</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Atypical antipsychotic</td>
<td>Yes, with exceptions</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Benzodiazepine</td>
<td>Not for acute CINV</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Prokinetic</td>
<td>Not for acute CINV</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>1st generation antipsychotic</td>
<td>Not for acute CINV</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Phenothiazine antipsychotics</td>
<td>Not for acute CINV</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Synthetic cannabinoid</td>
<td>Not for acute CINV</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Synthetic cannabinoid</td>
<td>Not for acute CINV</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Antihistamine</td>
<td>Not for acute CINV</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Antihistamine</td>
<td>Not for acute CINV</td>
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## Appendix D. Information of interest in EHR

<table>
<thead>
<tr>
<th>EHR System</th>
<th>Title of Note</th>
<th>Section of interest</th>
<th>Variable within note</th>
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</thead>
<tbody>
<tr>
<td><strong>Outpatient visits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescriber documentation</td>
<td>Follow-up Visit (Pediatric and Adult Oncology)</td>
<td>History of present illness (HPI)</td>
<td>• CINV assessed</td>
</tr>
<tr>
<td></td>
<td>Home Medication List</td>
<td>Problem list (active)</td>
<td>• CINV present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI medication prescriptions</td>
<td>• Free text from HPI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ICD-10 code for CINV</td>
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<td>• ICD-10 code for primary disease</td>
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<td>• ICD-10 code for antineoplastic visit</td>
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<td>Inpatient visits</td>
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<td>Pediatric Oncology Note</td>
<td>History of present illness</td>
<td>• CINV assessed</td>
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<td>Ob/Gyn Encounter Note</td>
<td>Problem list (active)</td>
<td>• CINV present</td>
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<td>Clinical summary (ICD-10 codes)</td>
<td>• Free text from HPI</td>
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<td>Hem/Oncology Attending Follow-up Note</td>
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<td>Nursing documentation</td>
<td>Ambulatory Nursing Assessment</td>
<td>GI symptoms</td>
<td>• Nausea/vomiting present (Y/N) (text)</td>
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<td>Emesis (volume)</td>
<td>• Medication given (Y/N) (Drug)</td>
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<td>Emesis (episode)</td>
<td>• Chemotherapy type</td>
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<td>Nursing Chemotherapy/Biotherapy Record</td>
<td>Chemotherapeutic and antiemetic agents administered in clinic</td>
<td>• Confirm class of emetogenicity is HEC</td>
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<td>Medication Administration Record</td>
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<td>• Appropriate regimen administered in clinic (Y/N)</td>
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<td>Nursing Discharge Note</td>
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