QUANTIFYING BURDEN OF TREATMENT FOR BREAST CANCER PATIENTS FROM CLINICAL ENCOUNTER DATA

By

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CHAPTER 1

Introduction

1.1. Preamble

Chronic illness is detrimental to a patient's quality of life both because of the symptoms of the illness itself, as well as the burden of treatment needed to combat the illness. The complexity of medical care today makes it difficult for healthcare providers to monitor a patient's capacity to receive care even though treatment overburden can impact disease outcomes. We hypothesize that the healthcare system could use quantitative measures of treatment burden to evaluate the impact of disease and interventions on cancer patients. In this thesis, we propose a framework for quantifying burden of treatment in patients with breast cancer from electronic health record (EHR) data. We use this framework to evaluate treatment burden in a population of breast cancer patients and to detect changes in treatment burden with changes in therapeutic protocols.

1.2. Minimally disruptive medicine

In an era where patients are increasingly responsible for managing their own healthcare, minimally disruptive medicine is a new paradigm where providers ensure patients are able to adequately handle the care they are prescribed(1). Minimally disruptive medicine deals with the tension between two competing factors: A patient's capacity to handle the work of receiving care, and the burden of their illness and treatment (2)(3). Several patient attributes help to increase their capacity to receive care. Personal, physical, emotional, social, environmental, and financial resources make patients more capable of achieving compliance with their treatment plans(4). For example, patients who have more financial resources, have access to transportation,

have flexible working hours, and who are literate will be more likely to handle more healthcare tasks(2).

On the other hand, burden consists of the hardships imposed by illness and the work of receiving care for that illness(5). Burden of illness includes symptoms that reduce a patient's ability to function such as fatigue, physical disability, or cognitive impairment(6). Burden of illness is typically well studied in medical literature. However, burden of treatment is not typically tracked or well understood in the medical community(7). Previous patient surveys have identified many factors that contribute to treatment burden and have categorized them in to three major themes: work patients must do to receive care, problem-solving and coordination, and factors that exacerbate perceived burden such as financial, emotional, and logistical challenges(8). Figure 1.1 illustrates the model of minimally disruptive medicine. A patient's disease contributes both to the burden of the illness itself and treatment burden to counteract the disease. When burden exceeds a patient's capacity to handle care, they are overwhelmed, typically leading to worsening outcomes. However, if patients are able to handle their care (ie. when capacity exceeds burden), they are able to fully comply with their treatment plan leading to positive health outcomes. Improved and worsening outcomes subtract and add respectively from burden causing a feedback loop that leads to recovery or increased morbidity.

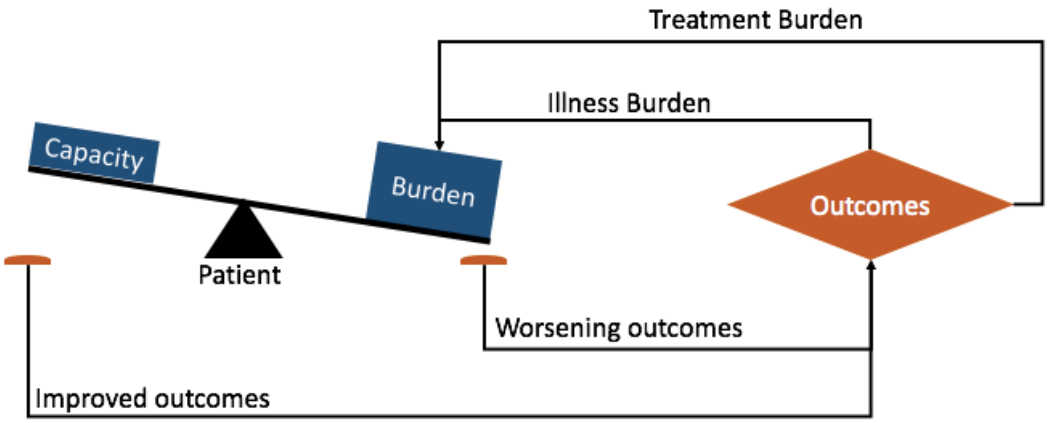


Figure 1.1. Illustration summarizing minimally disruptive medicine.

There is evidence that customizing care according to patient capacity is more than just making care convenient. A high burden can cause lower treatment plan compliance in patients with chronic diseases(9). Excessive treatment can also lead to wasted resources for the medical center, both from unnecessary procedures and from having to treat complications from noncompliance(10). Physicians who practice minimally disruptive care assess burden and tailor treatment plans that give a patient the maximum likelihood of recovery while taking into consideration the patient's limitations(1). To improve the effectiveness of this paradigm, providers and healthcare systems need reliable ways to identify overburdened patients and patient populations.

1.3. Comparison to similar domains

While itself a distinct research subject, burden of treatment has similarities to other healthcare research domains. Figure 1.2 shows the overlapping domains of quality of life, financial toxicity, burden of care and value-based medicine in relation to burden of treatment. One element of burden of treatment research that is not addressed in depth in any of these other domains is healthcare tasks.

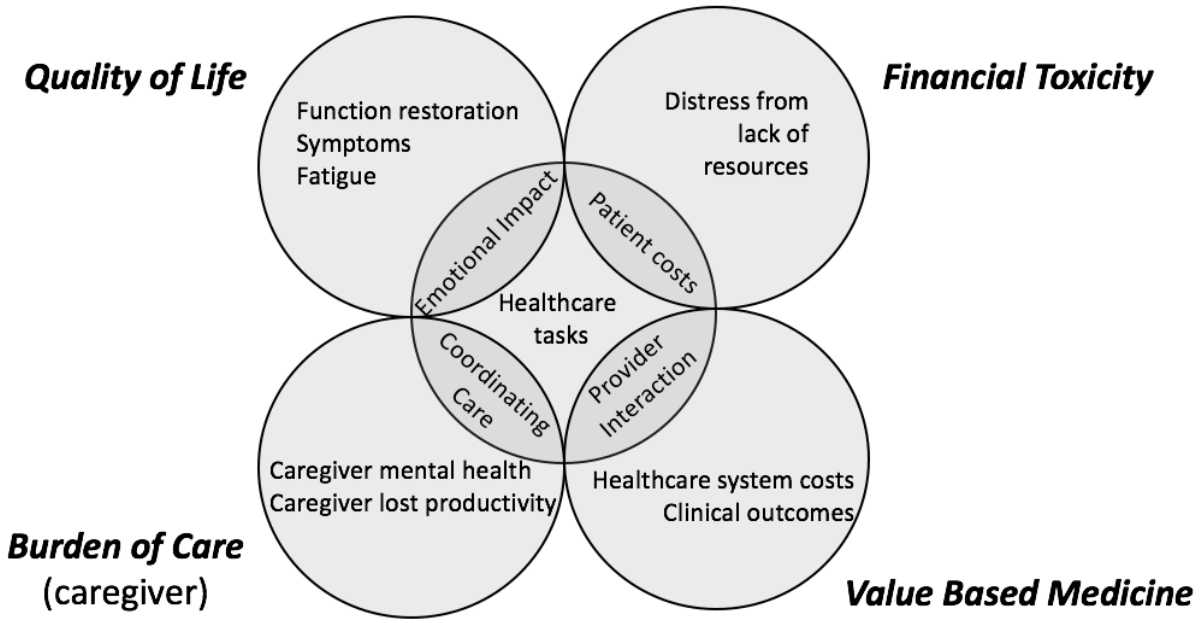


Figure 1.2. Factors common to treatment burden and other similar domains

1.3.1. Quality of life

Perhaps the most well researched of these domains is quality of life. Quality of life scores are typically clinical measures that determine what loss in function, if any, occurred during and after a specific illness and associated treatment(11). Some quality of life scores are for general patient care such as the SF-36(12), while others are disease specific such as the DQOL for diabetes(13) and the EROTC QLQ for cancer(14). These quality of life scores focus on factors such physical, cognitive and social function, pain, fatigue, and other symptoms(15). In the minimally disruptive medicine paradigm, quality of life factors may influence burden of treatment, but they are more directly related to patient capacity and illness burden.

There are some lessons from studies on quality of life that are applicable to our study of treatment burden. When studying quality of life, researchers have seen it is difficult to develop a single measure that adequately summarizes quality of life, since different patients may value return of different functions differently(16). When coming up with measures and treatment plans,

providers need to take into consideration patient preference and goals in order to accurately determine both quality of life and burden of treatment(17)(18)(19).

1.3.2. Burden of care

Although it sounds similar to burden of treatment, burden of care in medical literature refers to the burden that a patient's illness imposes on their caretakers, especially with regards to elderly patients(20). For example, caretakers and family members of patients with cancer often experience depression, uncertainty about the future, and disruptions to home or work life(21)(22). Although burden of treatment is focused on the patient, many factors affect their caregivers. Patients with cancer often want to be with their family and caregivers during appointments requiring the patient to coordinate schedules and transportation(23). Especially for terminal diseases such as cancer, patients need to provide emotional support and financial planning, which increases the stress associated with their disease(21).

1.3.3. Financial toxicity

Another recently discussed topic with ties to treatment burden specific to cancer is financial toxicity. Similar to how toxicity from chemotherapy can lead to complications in their care, financial distress from having to pay for cancer treatments can cause increased risk for mortality(24). The problem has gotten so serious recently that scores have been developed to evaluate the extent of financial toxicity in cancer patients(25). While direct financial costs are one aspect of treatment burden, financial distress also contributes to capacity. For example, cancer patients without the financial capacity to afford a full course of oral chemotherapy could be non-adherent to their medication plan due to high co-pays(24). Additionally, patients who cannot afford their care may divert funds for other necessities and have to apply for government assistance such as food stamps and temporary disability(26). These patients may also ask people

they know for financial assistance or apply for grants, further adding to the work and emotional stress of being a patient.

1.3.4. Value-based medicine

In an effort to reform payment structures in the healthcare systems and contain costs, some have proposed outcomes based payment models as opposed to the traditional fee-for-service models(27). Providers would be incentivized to maximize value of care by achieving all desired clinical outcomes while minimizing the cost of care to achieve those outcomes(28). Quality outcomes for breast cancer may include short term factors such as no nausea during chemotherapy, and long term outcomes such as remission and 5 year survival(28). While both value-based medicine and minimally disruptive medicine are focused on getting positive health outcomes, value-based medicine attempts to minimize costs to the healthcare organization without considering costs to the patient. It may be reasonable to conclude that decreased cost for healthcare systems translates to decreased burden for the patient. However, this correlation is not always clear. For example, in chemotherapy, oral regimens usually involve less time spent at the clinic than infusion regimens. However, there may be compliance or administration errors with home medications and the patient's out of pocket expense is sometimes much higher with prescription co-pays versus infusions. In value-based medicine, there is no measure focused on the financial and workload costs to the patient.

Nevertheless, attempts to implement value-based medicine may serve to decrease patient burden. With the current fee-for service model of healthcare, healthcare systems have incentive to perform as many procedures as possible, even if those procedures have little effect on improving outcomes, in order to maximize revenue. With value-based medicine on the other hand, healthcare systems are motivated to perform as few procedures as possible to achieve the

desired outcome to maximize their profit from their fixed payment. Value-based medicine could help align revenue incentives in a manner that decreases patient burden.

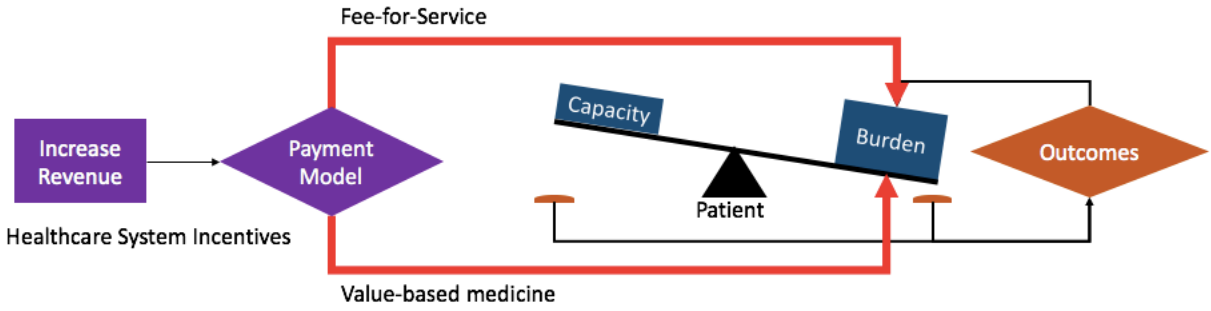


Figure 1.3. Aligning incentives for healthcare systems to positively affect patient burden.

As such, the literature in minimally disruptive medicine and similar domains has started to characterize treatment burden. However, none of these studies have addressed a method to describe the extent to which healthcare tasks affect the work patients must complete. Additionally, previous scores meant to quantify factors similar to treatment burden have required patient reported data(15).

1.4. Treatment burden in breast cancer

Breast cancer patients often undergo intense, multi-modal treatments resulting in diminished quality of life(29)(30). Unlike diseases previously studied for burden of treatment like diabetes, cancer care is more episodic. These care episodes can require intense treatment over the course of months and years(31). A nationwide study showed that among patients undergoing chemotherapy and radiotherapy, 28% had to schedule appointments to treat side effects, 77% had to arrange for caregivers to accompany them to their appointments, and 43% had some impact on their professional lives(31). Additionally, oncology patients are typically older and have many comorbid conditions that add to the complexity and burden of treatment(32).

One reason why burden of treatment measures are needed in breast cancer care is because of the many choices patients have for treatment paths. After diagnosis, providers must discuss with patients the benefits and risks of different treatment options such as surgery (lumpectomy or mastectomy), radiation therapy, chemotherapy, immunotherapy, hormone therapy, or some combination of these(33). Some of these options may have clear therapeutic advantages for certain patients. However, when deciding between options like lumpectomy with radiation and mastectomy that have similar survival rates(34), it may be unclear which of these choices would burden the patient less in the short term with treatment, and in the long term with complications and recurrence. In previous studies, treatment decisions for patients with breast cancer were significantly influenced by the frequency of the care and how specific (i.e. quantitative) information given by the provider was(35). We believe that a quantitative approach for assessing treatment burden could inform interventions to help minimize treatment burden for patients with breast cancer.

1.5. Measuring burden and capacity

Previous research on the topic of treatment burden has focused on surveys to create scores for patient work, and to create a framework for researching and delivering minimally disruptive medicine(36). In an online survey of 1053 patients, researchers created a taxonomy of factors that contribute to the burden of treatment including healthcare tasks and situational factors that exacerbate a patient's work (37)(38). Tran et. al. also developed and validated the Treatment Burden Questionnaire (TBQ), a survey instrument designed to assign an global score for treatment burden(38)(39). Some of the items on the TBQ address healthcare tasks themselves such as the number of times patients must take their medication per day, or the frequency and duration of doctors' visits and lab tests. Other factors are more subjective such as the impacts of

healthcare on social relationships or how often healthcare reminds the patient of their health problems. The group that developed TBQ showed that their global score was significantly correlated with quantitative measures workload variables such as number of hospitalizations in the last year, number of different physicians, number of medication tablets taken per day, and number of medical appointments per month. Disease specific questionnaires have also been developed to assess the burden of treatment in specific chronic conditions such as chronic heart failure(40), post stroke(41), and end stage renal disease requiring dialysis(42). While these surveys are effective in defining treatment burden, they still rely on patient reported surveys for their data, which would not enable large scale population studies of burden or automated monitoring to identify overworked patients who may need intervention.

One factor of treatment burden that is being quantified in public health informatics is with study of healthcare access. Using Geographical Information Systems (GIS), public health informatics studies have calculated driving distance to the nearest medical center and attempted to correlate geographic factors to healthcare utilization such as mammogram screening for breast cancer patients(43). Similarly, burden of treatment studies will be able to use GIS software to determine the commute time to and from the medical center for procedures as a major contributor to the work patients must put into their care.

A recent study also sought to quantify the counterweight to burden, capacity. Boehmer et. al. used a bevy of previously developed psychosocial metrics to assess capacity in 137 patients on dialysis(4). Some of these surveys include CD-RISC-2 for patient resilience, SF-36 for emotional well-being, PROMIS Short Form 4a for social capacity, and the CAHPS Patient Health Care Home Survey for environmental capacity. They correlated these capacity factors with illness intrusiveness and found that physical, emotional, and financial well-being were most

important for patients to feel they were in control of their treatment. Developing an automated method to quantify capacity may be a challenge due its subjective nature. Whether patient reported or derived from the EHR, it is essential for future work to complement burden measures with capacity metrics so that providers can balance the two for patients leading to better outcomes.

1.6. Anomaly detection in healthcare

One important use for treatment burden measures is to identify outliers who may require help managing their care. Healthcare organizations have used anomaly detection in public health for disease surveillance. For example, the University of Alabama developed a method to quickly identify hospital acquired infections from laboratory data by identifying patterns of transmission that may not be immediately evident to healthcare providers(44). A Pittsburgh based team also used rule-based anomaly detection to identify disease outbreaks based on patterns in clinical data in local emergency rooms(45). In both cases, anomaly detection enabled the respective healthcare systems to identify outliers that required intervention but that were difficult for healthcare professionals to notice. Similarly, patients experiencing high treatment burden may not be immediately identified by their providers, especially if these appointments span multiple departments.

Researchers have also used outlier detection methods to scan clinical trial reviews for significant relationships between chemotherapy drugs and adverse events(46). Lou and Cisler used boxplots to visualize the distribution of incidences of adverse events by common chemotherapy drugs from clinical trial literature. Using Grubbs' test, they identified drugs where the association with a given type of adverse event was significantly higher than other drugs. Using this outlier detection method, this study successfully aggregated previously published data

from a large set of publications to discover novel associations without having to conduct any additional clinical trials. With treatment burden research, it is possible to prospectively collect data from patients about their healthcare tasks during their cancer care as studies have done in the past(31). However, our study proposes that the data already existing in various sources in the EHR would allow us to assess burden of treatment in many patients with cancer.

Anomaly detection is also used by providers to identify high-risk patients. Many studies have attempted to develop models that predict hospital readmissions(46). Readmissions are of interest to payers and healthcare organizations due to their financial cost the hardship they place on patients. Patients who have high treatment burden in both the inpatient and outpatient setting also endure disruptions to their personal lives and financial costs. Having a tool that flags overburdened patients could be useful to identify those patients quickly and to intervene accordingly.

1.7 Interventions related to treatment burden

Treatment burden measures derived from the electronic medical record would be useful for evaluating the effectiveness of new treatment protocols or healthcare operations interventions that aim to reduce treatment burden. These measures could also assist with patient and provider treatment plan decisions. To enable the practice of minimally disruptive medicine, healthcare systems could leverage informatics methods that use medical record data to make burden of treatment data useful for the healthcare delivery team. One of the uses of EHR data is to enable retrospective and prospective comparative effectiveness research(47). Before EHRs were available, researchers would have to set up a clinical trial to compare different treatments, which required recruiting patients, setting up controls and in-person follow-ups with patients. EHRs enable researchers to collect that data passively through records already stored electronically for

patient care, often with no disruption to the provider or patient. EHRs also enable comparative studies that investigate previous protocol changes with the rapid collection of a large number of patients(48).

A treatment burden measure would be useful when assessing treatment options in clinical trials. Historically, trials in cancer compare clinical outcomes such as disease free survival and recurrence(49). In recent clinical trials, researchers have shown that pathological complete response, which is the absence of cancerous tissue after treatment, is correlated to disease-free and overall survival(50). Since pathological complete response can be evaluated immediately after treatment, it has become the standard measure in determining therapeutic efficacy in breast cancer clinical trials(51). Clinical trials also document patient-reported outcomes such as anxiety, physical function, pain, and fatigue(52). With chemotherapy, clinical trials report commonly occurring side effects from toxicity such as diarrhea, alopecia, leukopenia, thrombocytopenia and neutropenia(53)(54)(55). We believe that burden of treatment is also an important measure that should be incorporated into clinical trials. As discussed, the work of receiving care can have an impact on patient burden just as illness and side effects do. In Chapter 4 of this thesis, we demonstrate a method of comparing treatment burden for chemotherapy protocols that could be replicated for clinical trials.

The ultimate goal of our research is to positively impact the delivery of healthcare. We want to enable providers to practice minimally invasive medicine by developing tools that weigh treatment plans against patients' capacity to handle that treatment. Clinical decision support systems process electronic health record data and present information through calculators, alerts, and reminders to healthcare providers(56). Although the creation of a clinical decision support tool for treatment burden assessment is beyond the scope of this work, it is important for us to

consider how to develop measures and analyses for treatment burden that are useful for clinicians. As such, it is important to consider how to implement and evaluate the impact of integration of a quantitative measure of treatment burden within the context of the workflow of a healthcare delivery team with the goal of providing decision support to minimize treatment burden. Additionally, we must design any patient-facing tools such as mobile applications that help patients monitor or cope with burden in such a way that they are useful to patients(57).

Healthcare organizations could use treatment burden measures to evaluate the efficacy of healthcare operation interventions. Hospitals have tried to implement lean practices borrowed from the automotive industry as a way to increase efficiency and improve quality(58). Lean management requires collection of clinical and administrative data like clinic throughput, and medical errors(59). Hospitals have used logistics methods such as scheduling optimization in chemotherapy(60) and other healthcare settings to maximize provider utilization(61). While these methods have been shown to improve operations in the medical center, they should also be evaluated for how they impact work for the patient.

Burden of treatment also plays a part in defining the successes or failures of precision medicine. Initiatives in precision medicine seek to tailor treatment strategies to take into consideration individual variability in genetic, clinical, environmental, and molecular factors(62). The paradigm of minimally disruptive medicine uses some concepts from precision medicine in that providers need to tailor the amount of care given based on characteristics of the patient that show they have the capacity to handle the care. However, an even more powerful application of a burden of treatment measures is to assess changes in practice championed by precision medicine for their effect on patient work. Precision medicine research in breast cancer has identified biomarkers that make the cancer vulnerable to certain targeted therapies(63).

These targeted therapies are more effective and require fewer treatments for the patient(64). In order to quantify the effect of these precision medicine diagnostics on the patient experience, the healthcare community needs burden of treatment measures.

CHAPTER 2

Quantitative Measures for Treatment Burden from Encounter Data

2.1. Introduction

This chapter proposes a method to quantify one of the more reliable contributors to treatment burden in patients with breast cancer: clinical encounters. While appointments only contribute to part of a patient's overall treatment burden, time and effort spent coordinating, traveling for, and waiting for care were among the most commonly mentioned contributors to burden in a survey of 1053 patients with chronic disease(37). Among these patients who responded to an online survey, 50% mentioned that some burden stemmed from treatment appointments and follow-up compared to 29% who felt burdened by paperwork and 13% that mentioned learning about their condition. The majority of patients were also burdened by managing medications and lifestyle changes such as diet changes, exercise, and quitting smoking. In the treatment burden questionnaire (TBQ), encounter related burden factors were among the most highly correlated with the overall TBQ score(39). Unlike diabetes where most care is performed by the patient away from the medical center, cancer care is highly dependent on procedures (such as chemotherapy, radiotherapy, and surgery) that are well captured by outpatient encounters. Hospital admissions are also of interest to patients and hospital administration. Admissions are frequent and often unexpected in patients with cancer (65). Although inpatient time was typically not mentioned in previous burden of treatment literature, admissions are disruptive to patients and their caregivers. To our knowledge, no previous studies have used data from electronic health records (EHRs) to assess treatment burden in patient populations. By using appointment and admission data, our evaluation of treatment burden is reliable, reproducible, and scalable given accurate electronic records.

2.2. Healthcare tasks in the EHR

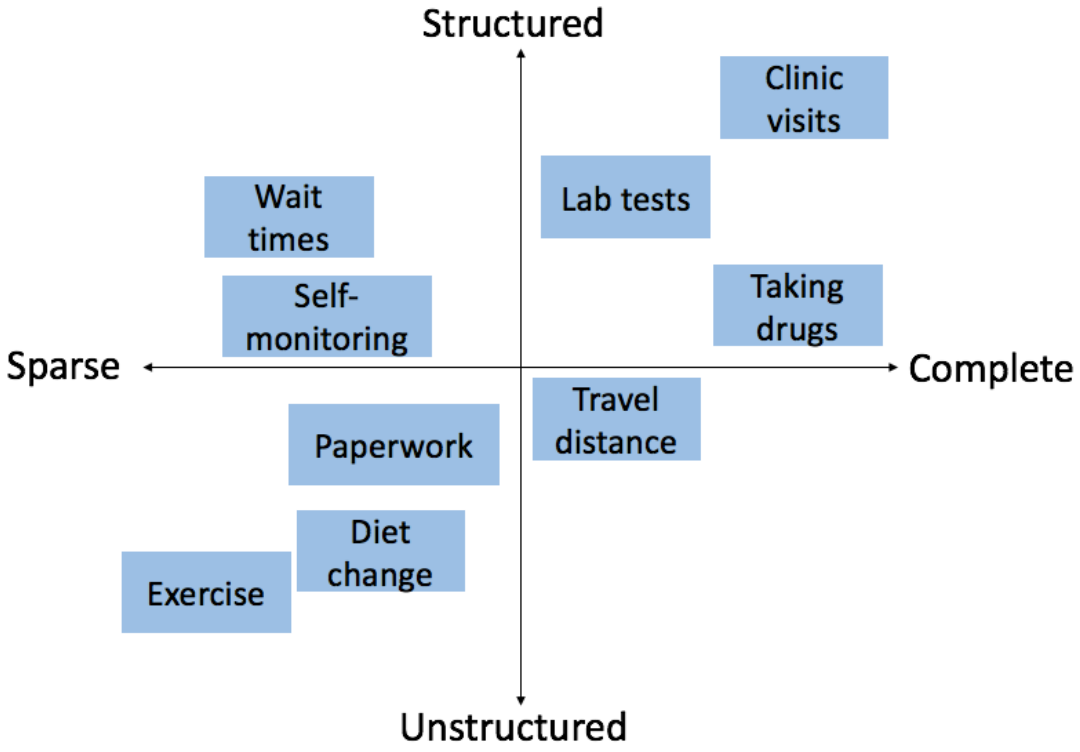


Figure 2.1. Relative completeness and structure of data elements related to factors of healthcare tasks. Highly structured and complete elements may be amenable to automated extraction and quantification from the electronic health record.

Research using EHR data is most effective when that data is structured and complete(66)(67). Figure 2.1 displays several healthcare tasks identified by Tran et. al.(37) and Eton et. al(36). For tasks with data available in the EHR, we evaluated them for approximate completeness and structure of data in the EHR. Treatment burden elements in the top-right quadrant of Figure 2.1 such as clinic visits and medications are both highly structured and highly complete by virtue of their relation to billing. These top-right elements are more reliable measures than elements in the bottom-left that are unstructured and less available. For example, a patient's exercise program is less likely to be captured in an EHR but may be recorded in other

systems managed by the patient outside the EHR. While healthcare institutions may differ in how these factors of treatment burden are recorded, many of these data elements are available across different implementations of clinical information systems.

2.3. Burden of treatment measures

Our goal was to create and evaluate several measures of treatment burden derived from appointment records. Since we are interested in the complete burden patients experience, we collected encounter data for all types of appointments, including non-cancer related encounters, from the start to the end of their care episode. The measures derived from the encounter record represent different aspects of burden that patients experience as part of their care. We extracted outpatient appointment data from the Epic scheduling system that had been in use at Vanderbilt University Medical Center (VUMC) since 1997. Hospital admission and discharge data was extracted from the Medipac system with data going back to 1984.

2.3.1 Appointment time

Our first measure of treatment burden was total appointment time. We calculated the time spent in appointments as the sum of the lengths of all appointments over a given time period. Time spent in appointments requires a high level of activity by the patient. Patients receiving breast cancer treatment in our study underwent not only cancer related procedures such as chemotherapy infusions and radiation therapy but also imaging procedures, laboratory draws, and non-oncology appointments. Appointment time represents their direct interaction with the healthcare system.

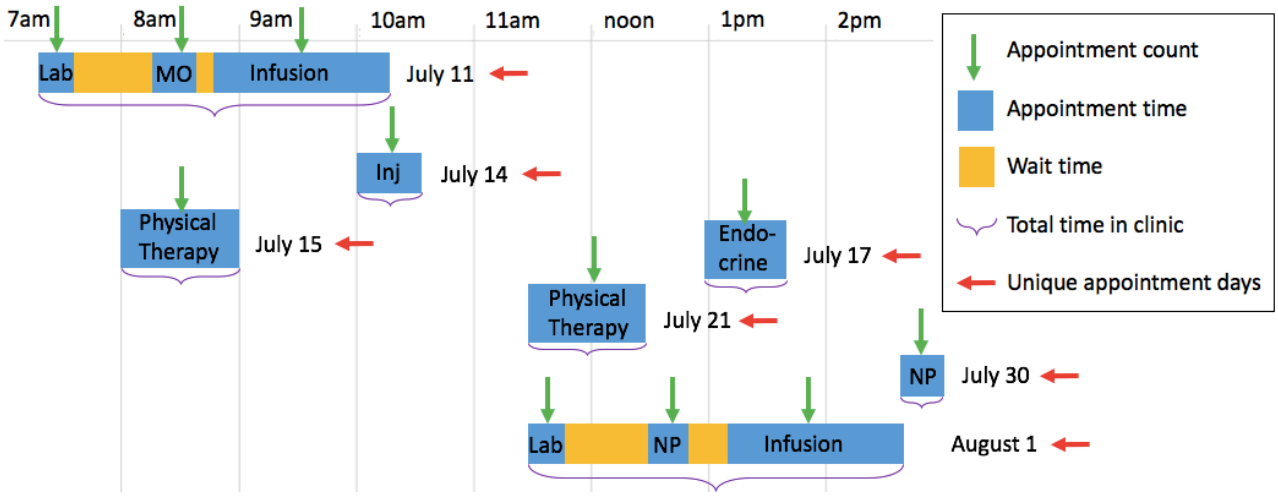


Figure 2.2. Burden of treatment measures for an example patient. This example breast cancer patient had about 9 hours of appointments, 11 appointments, 2.25 hours of waiting, 11.25 total hours in clinic, and 7 unique appointment days over two weeks chemotherapy treatment. MO= Medical Oncologist, Inj = Injection clinic, NP = Nurse Practitioner,

2.3.2 Appointment count

Appointment count was another measure that represented a similar but distinct dimension of treatment burden. We counted the number of appointments over the course of each patient's care episode. Each individual appointment is a unit of work the patient must perform. Every individual appointment has associated tasks such as checking in at reception, waiting for the appointment to begin, and engaging with providers and other staff.

2.3.3 Wait time

We extrapolated that wait time was the time between scheduled appointments if a patient had more than one appointment in a given day. Time spent waiting between appointments represents wasted time for the patient. Some wait time is necessary for upstream dependencies for treatment. For example, the laboratory needs time to process blood samples to determine whether a patient can receive chemotherapy. However, this time brings no value to the patient and can cause anxiety and frustration for patients while waiting to receive care.

2.3.4. Total time in clinic

To approximate the total time spent in clinic including waiting time, if a patient had more than one appointment in a day, we calculated the time from the beginning of the first appointment to the end of the last appointment of the day. Although derived from appointment time and wait time, the total time patients spend in clinic captures another dimension of treatment burden. Patients and their caregivers who continue their employment during treatment must request time off in at least the amount of their total time in clinic. If patients are caring for family members, they may need to request substitutes or hire professional caregivers during the time they are receiving care.

2.3.5. Unique appointment days

Unique appointment days represent the work of coordinating and commuting to the clinic. Patients who receive cancer care often request friends or family join them, which places a burden on the patient to coordinate schedules. For patients who do not leave home often, each unique appointment day adds to the stress and effort of getting ready to leave home and traveling to the medical center.

2.3.6 Admissions

We also collected data on whether patients were admitted to the emergency room or inpatient unit sometime over the course of treatment, and their overall length of stay during those admissions. Some admissions are planned, such as those for immediate post-operative monitoring, while other admissions may be related to severe health complications from the patient's underlying disease or their cancer treatment, such as uncontrolled nausea and vomiting from chemotherapy toxicity(55). Patients who are admitted during their care episode experience

the highest level of potential health risk and disruption to patients' daily lives and so changes in treatment protocol should look to minimize complications that lead to admissions.

2.4. Discussion

Using the appointment record at VUMC has limitations. While the appointment record should be accurate and complete due to its association with billing, it does not always reflect exactly what happened in the clinic. For the purpose of this study, time between appointments is a heuristic for actual wait times. Our method of determining the amount of time spent in clinic is a conservative estimate. It does not take into consideration situations where patients arrive early, appointments start late, patients leave between appointments, or appointments end earlier than the time allotted. Using data from systems that track patient arrivals, departures, and movements within the clinic, such as VUMC's outpatient whiteboard(68), could enable more detailed analysis of patients' total time in clinic. However, since these systems rely on manual updates of patient movements, they could have limited accuracy. To address this, some healthcare systems have reported use of real time locator systems (RTLS) to pinpoint the location of patients as they move through the medical center(69). These advanced techniques could provide more precise data about patient burden during patient encounters, but would be difficult to generalize to other institutions that do not have similar infrastructures for patient tracking. Another limitation of using only VUMC's encounter data is that most patients do not receive all of their care at a single institution. Our approach acknowledges this, and appreciates that this may account for a large range of treatment burden among patients with similar diagnoses.

Despite these limitations, a major advantage of this approach for assessing burden of treatment is its simplicity of calculation and generalizability to other healthcare organizations who all have electronic appointment and admission records. Since Stage 1 Meaningful Use was

enacted, healthcare systems are incentivized to maintain accurate patient encounter records(70). Therefore, any healthcare organization could use scheduling data to approximate patient burden. On the other hand, some limitations impede direct comparisons between our study population and those at other institutions. Other institutions may record appointments differently than VUMC. For example, another healthcare system with the patient in Figure 2.2 could have just one very long appointment that incorporates the lab, medical oncologist, and infusion visits. Meanwhile at VUMC, each of those encounters is recorded as a separate appointment. Comparing patient populations within that institution would still be possible but comparing certain features of treatment burden across institutions might be challenging.

2.5 Conclusions

Treatment burden measures derived from encounter data only capture one aspect of the work that patients need to perform to receive care. Nevertheless, factors such as total time in clinic, unique appointment days, and admissions represent a large portion of burden, particularly for cancer patients. These factors derived from electronic appointment records are also highly complete and reliable making this method generalizable at other institutions.

CHAPTER 3

Evaluating Treatment Burden in Breast Cancer Patient Subpopulations

3.1 Introduction

A useful quantitative measure of treatment burden must be able to differentiate between patient populations that are expected to have differences in their intensity of treatment. To evaluate this capability of our measures, we applied them to a population of breast cancer patients with early stage (I-III) disease. Breast cancer patients at Vanderbilt with stage III disease typically have much more intensive, multimodal treatment than those with stage I or stage II disease. We thus hypothesized that patients with stage III cancer would have a higher treatment burden than patients with stage I or stage II cancer given the more aggressive therapy they receive for higher risk disease. Breast cancer treatment given with curative intent is typically delivered within the first 18 months after diagnosis. Therefore, we likewise hypothesized that the burden of treatment would be greatest in the first few months after the date of cancer diagnosis, and that this burden would decrease over time.

3.2 Methods

We applied the treatment burden metrics described in Chapter 2 to a population of breast cancer patients at Vanderbilt University Medical Center (VUMC). The goal of this analysis was to investigate whether there was differentiation in number of appointments, appointment time, wait time, total time spent in clinic including wait time, number of admissions, and total inpatient length of stay between breast cancer patients with stage I, stage II, and stage III disease.

3.2.1. Study population

The patient cohort for this study was chosen from the VUMC Cancer Registry since those were the patients who were diagnosed and receive all or part of their first course of treatment at our institution. We collected 18 months of encounter information from all stage I-III breast cancer patients who were diagnosed over a 17-year period between January 1, 1998 and June 1, 2014. To facilitate comparison between sub-populations of patients that received the majority of their care at our institution, we included only patients with at least three appointments from both a Vanderbilt medical oncologist and a Vanderbilt surgical oncologist in the first 18 months after diagnosis. We determined which appointments were with a medical or surgical oncologist by mapping their national provider identification number with their specialty in the national patient identifier (NPI) data dissemination file(71).

Among the 8161 patients with breast cancer in the VUMC Cancer Registry, 5661 had a date of diagnosis between January 1, 1998 and June 1, 2014. Among these, 4152 patients had stage I-III disease at diagnosis. After collecting 18 months of appointments after the date of diagnosis for these patients, we found that 904 had more than three appointments with a medical oncologist and a surgical oncologist at VUMC (Figure 3.1).

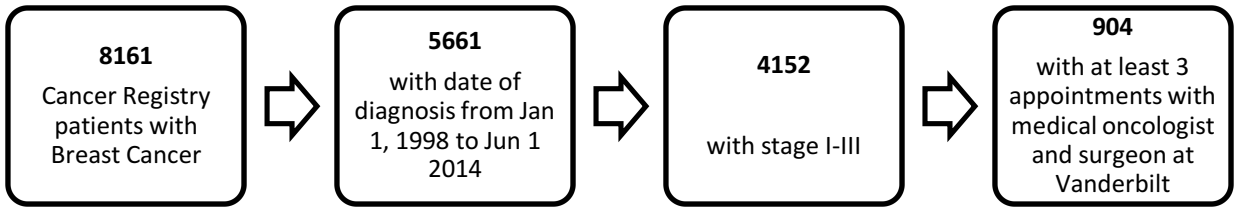


Figure 3.1. Cohort selection

3.2.2. Analysis

We compared the distributions of each treatment burden measure over 18 months by stage. We used an Kruskal–Wallis H test to see if there was a significant difference between

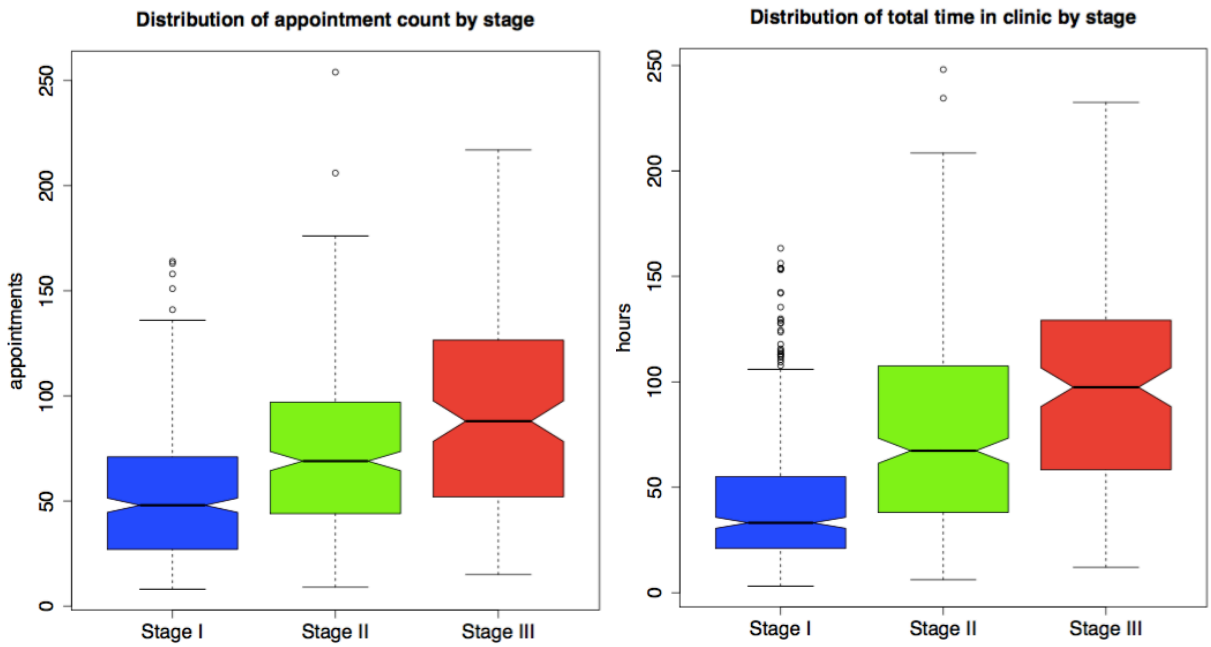
stages I-III for each of these metrics. We compared the estimated time spent in clinics by month over 18 months by stage. We also plotted the time spent in appointments by department for all patients over 18 months. The Vanderbilt Institutional Review Board approved this study and granted a waiver of consent since we analyzed a large population of patients in aggregate (IRB #151003).

3.3. Results

Table 3.1 summarizes the clinical encounter burden by stage. Among the 904 patients in the final cohort, 419 had stage I, 337 had stage II, and 148 had stage III disease. Across all stages, the median patient in our cohort had 59 appointments on 39 unique appointment days, spent 2.7 hours in clinic per month, and was never admitted over the 18 months after diagnosis. The median stage III patient had the greatest number of appointments (88), the greatest amount of time spent in clinic per month (5.4 hours), and the greatest number of hospitalized days (1.2). Stage II patients had the second greatest totals in each of these parameters and stage I patients had the least. The H tests for all of the metrics were significant with p-values less than .001.

Table 3.1. Summary of clinical encounter burden for breast cancer patients by stage with H test p-values comparing the difference between stage I, stage II, and stage III.

Treatment Burden Factor by Breast Cancer Stage		Stage I	Stage II	Stage III	Stage I-III	H test p-value
Number of patients		419	337	148	904	N/A
In first 18 months after diagnosis **Median** (IQR)	Number of appointments	**48** (27-71)	**69** (44-97)	**88** (52-125)	**59** (35-89)	< .001
	Unique appointment days	**34** (17-54)	**43** (26-64)	**49** (30-85)	**39** (22-61)	< .001
	Hours of appointment time	**20** (12-32)	**41** (23-67)	**60** (37-83)	**30** (16-58)	< .001
	Hours spent waiting between appointments	**13** (8-23)	**25** (14-40)	**33** (19-50)	**19** (10-34)	< .001
	Hours spent in clinic	**33** (21-55)	**67** (38-107)	**97** (58-129)	**49** (28-94)	< .001
	Hours spent in clinic *per month*	**1.8** (1.2-3.1)	**3.7** (1.9-5.9)	**5.4** (3.2-7.2)	**2.7** (1.6-5.2)	< .001
	Number of unique admissions	**0** (0-1)	**1** (0-1)	**1** (1-2)	**0** (0-1)	< .001
	Total inpatient length of stay (days)	**0** (0-1.2)	**.13** (0-2.5)	**1.2** (0-4.5)	**0** (0-2.2)	< .001



Figures 3.2 and 3.3. Distribution of total number of appointments over 18 months by breast cancer stage (H test p-value <.001), and total time in clinic over 18 months by breast cancer stage (H test p-value <.001). The dark horizontal line for each boxplot represents the median and the colored box represents the interquartile range (IQR) (25th to 75th percentile). The "whiskers" extend to 1.5 times the IQR or to the minimum or maximum value, whichever is closer. Any data points outside the whiskers are outliers and are represented individually as circles.

The boxplot in figure 3.2 further shows that the median and interquartile ranges of the number of appointments is greatest for patients with stage III disease followed by stage II and stage I. There were five outliers for stage I patients with an unusually high number of appointments while there were two outliers for stage II patients. Figure 3.3 shows that the median time spent in clinic was greatest for stage III patients followed by stage II and stage I. There are twenty-six outliers for stage I patients in time spent in clinic and two for stage II patients.

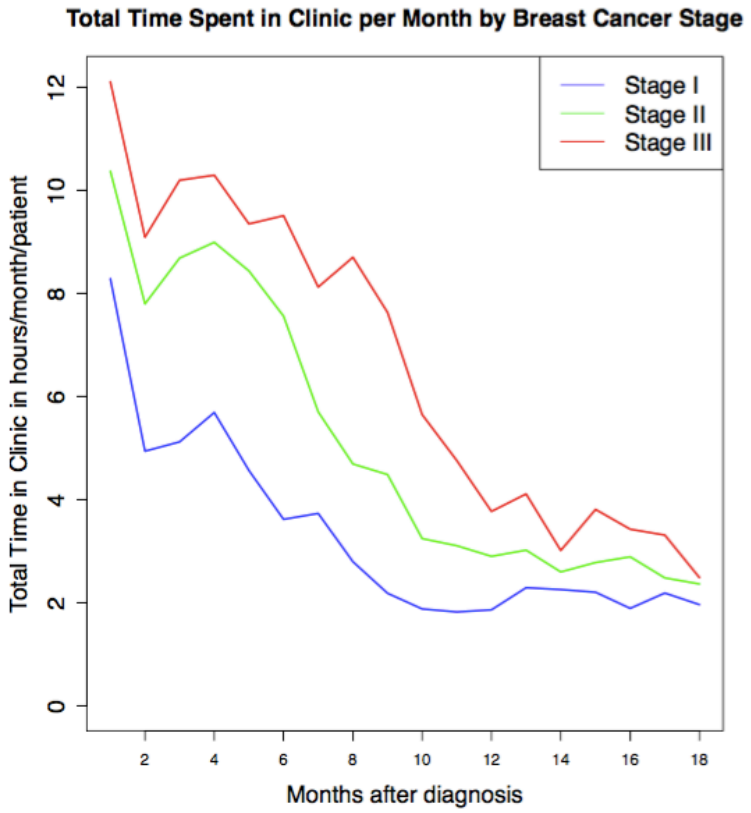


Figure 3.4. Total time spent in clinic by breast cancer stage over 18 months

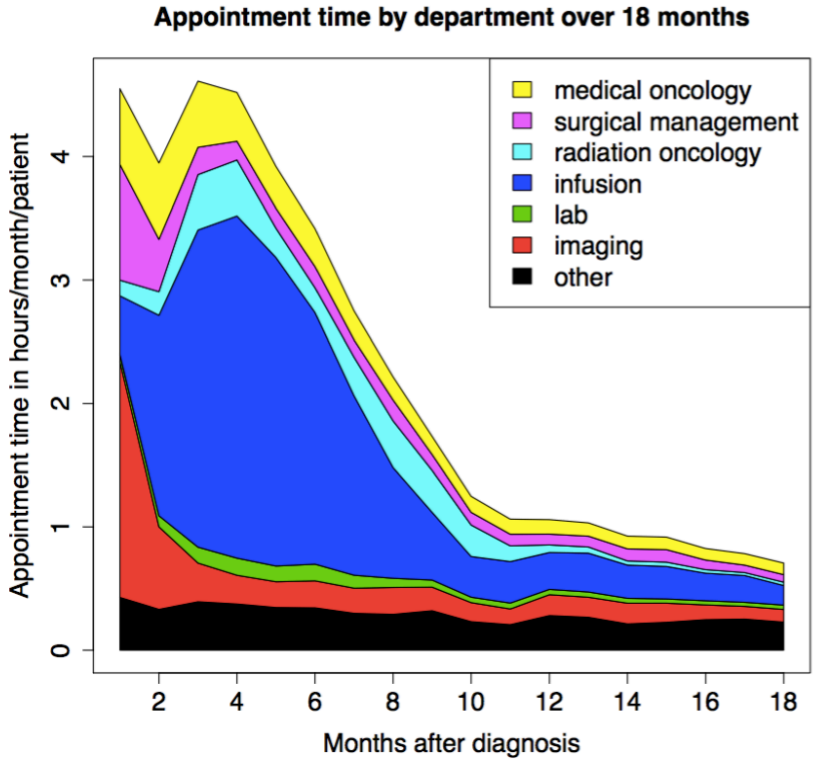


Figure 3.5. Appointment time by department over 18 months for all patients

Over the course of 18 months after diagnosis, the average total time spent in clinic per patient decreased (figure 3.4). In the first month of treatment, stage I patients spent on average 8 hours in clinic while stage II and III patients spent 10 and 12 hours respectively. All three stages saw a decrease in time spent in clinic in the second month but then had an increase in the third and fourth months. In each month after diagnosis, the average time spent in clinic was greater for stage III than stage II or stage I breast cancer patients, although this difference was not statistically significant for any given month. Figure 3.5 shows that radiology imaging appointments made up a significant portion of appointment time in the first couple months and decreased rapidly after date of cancer diagnosis. Infusion appointments made up the majority of appointment time from 3-7 months after diagnosis. Medical, surgical, and radiation oncology appointment times were greatest first six months after diagnosis and tapered as time went on.

3.4. Discussion

The boxplot in figure 3.2 is a good example of how healthcare systems can use appointment data as a proxy for treatment burden to identify outliers. In our population, a provider would notice that there are five stage I patients who had around 150 appointments in an 18-month period. A patient care team for one of those patients could investigate whether the appointments are appropriate. If that care is necessary, the healthcare system may look into ways to help ameliorate burden such as home visits or transportation assistance.

Understanding treatment burden can aid in delivering the right amount of care that is prioritized to what each individual can handle. When patients are newly diagnosed with stage I-III breast cancer, Figure 3.3 could help them anticipate how much time they will need to devote to coming to receive care and how much time they will need to take off from work. Future work could further divide our cohort into patients who chose different treatment paths such as

prophylactic contralateral mastectomy followed by reconstruction compared to lumpectomy with radiation therapy. Showing the treatment burden of similar patients could help educate patients about treatment options and their trade-offs.

Focusing on outliers in appointment burden could also identify opportunities for improved care coordination and more convenience for the patient. For stage I patients in figure 3.3, there are many more outliers for total time spent in clinic than for count of appointments in Figure 3.2. Since Figures 3.2 and 3.3 visualize the same population of patients, an increase in the number of outliers means that some patients who are outliers in time spent in clinic either have longer appointments or more time between their appointments. These patients would be candidates for care coordination interventions such as arranging their appointments closer together on the same day, or assigning them to a medical home clinic.

Figure 3.5 is an example of a visualization that healthcare organizations could use for resource planning. For every patient diagnosed with breast cancer this month, we can predict that the infusion center will need to have space, equipment, and staffing for an infusion chair for 2-3 hours three months from today. For resource constrained departments such as radiation therapy, knowing when patients diagnosed today will require their services could help them to prepare the staffing and other resources necessary for the increased demand.

There were several potentially confounding factors that we attempted to control for in our cohort selection. The first and most significant is that we had to determine which patients received their first course of treatment at VUMC. Although the cancer registry had information about which providers saw patients in the registry and what institutions they were from, the availability of that data was inconsistent. We decided on a data driven approach where we defined patients as having received their first course of treatment at VUMC if they had at least

three appointments with both a medical oncologist and surgeon from VUMC in the first 18 months of treatment. This constraint cut our cohort by more than 75%, but enacting the constraint was necessary to ensure that analysis focused on patients receiving care where we had more complete data on their encounters. We limited our analysis to stage I-III patients for a similar reason. Stage 0 and incurable stage IV patients have very different patterns of care making them less comparable in the first 18 months of treatment to stage I-III patients. We chose 18 months as the interval for analysis since a typical course of treatment occurs within that time frame and there is a very low risk of disease recurrence during this time(72).

Another limitation of this study is that we were not able to address missing data from patients lost to follow-up during the 18-month time span, or for care patients received outside of our institution. Furthermore, during the 17-year period where we observed our patients, there were changes in the way appointments were recorded in the system. There was a gradual increase in appointments per patient due to an increased number of departments using the scheduling system. The effect of this increase in appointment capture should have been minimal on the analysis since they would be equally distributed across patients in the different stages.

3.5. Conclusions

By describing and visualizing burden of treatment in a population of breast cancer patients, we believe this study helps providers deliver minimally disruptive medicine by identifying outliers who may need interventions to help decrease their burden. Quantifying burden of treatment for a given disease would also be useful for educating patients who are newly diagnosed so that they are prepared for the work ahead of them. Additionally, understanding the trend of utilization by department allows healthcare systems to ensure resources are available for future treatments at the time a patient is diagnosed.

CHAPTER 4

Evaluating Burden of Treatment with Changes in Chemotherapy Protocol

4.1 Introduction

New developments in treatment protocols have increased patient survival across all cancer types since the 1990s(73). As survival improves, patients could be more concerned with the convenience and quality of their care. In cancer treatment, there are many choices that patients and providers have to make based on the patient's disease and goals(17). Providers could use treatment burden measures to compare two or more treatment protocols for their impact on patients. Advertisements for medical services and medications often tout treatment burden reducing potential by "saving you a trip to the doctor" or needing just "one pill a day". Nevertheless, these claims are not typically substantiated with quantitative assessments of patient experience. Patients, healthcare providers, and healthcare delivery systems, need a method to track the patient work associated with cancer care to better inform treatment decisions. Additionally, changes in treatment protocols need to be evaluated for how they impact treatment burden.

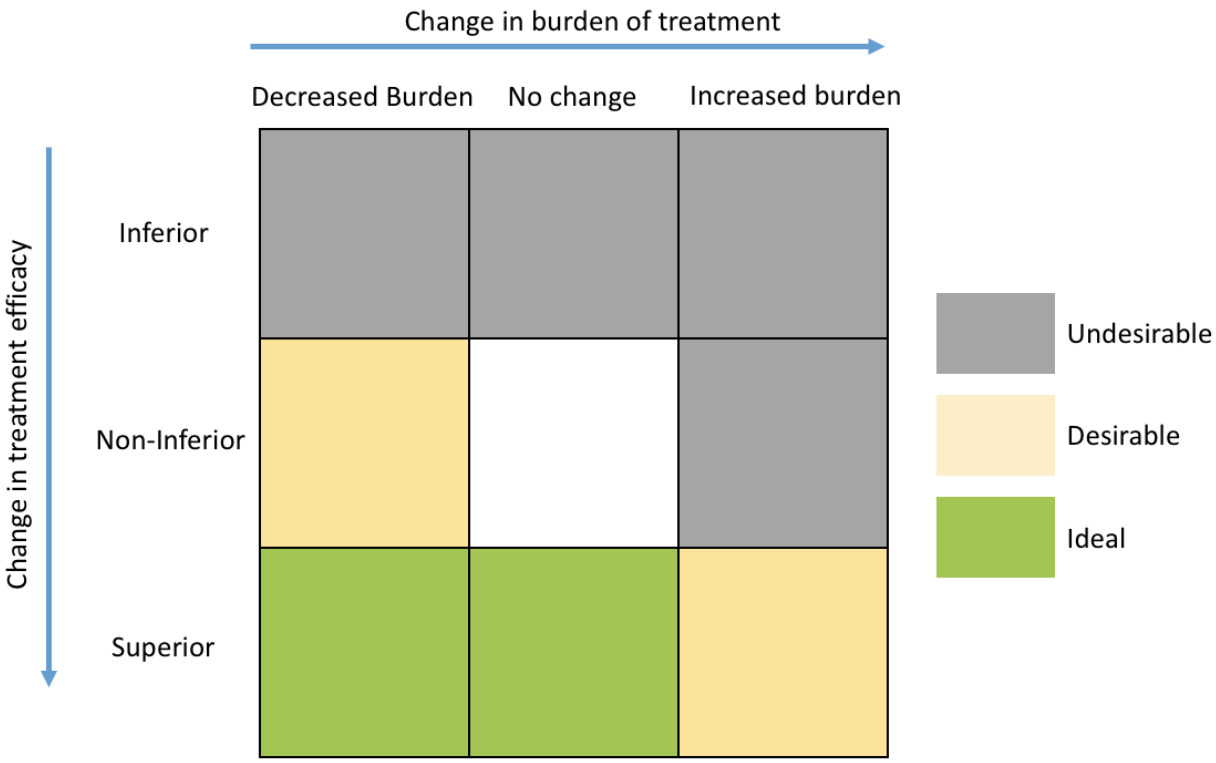


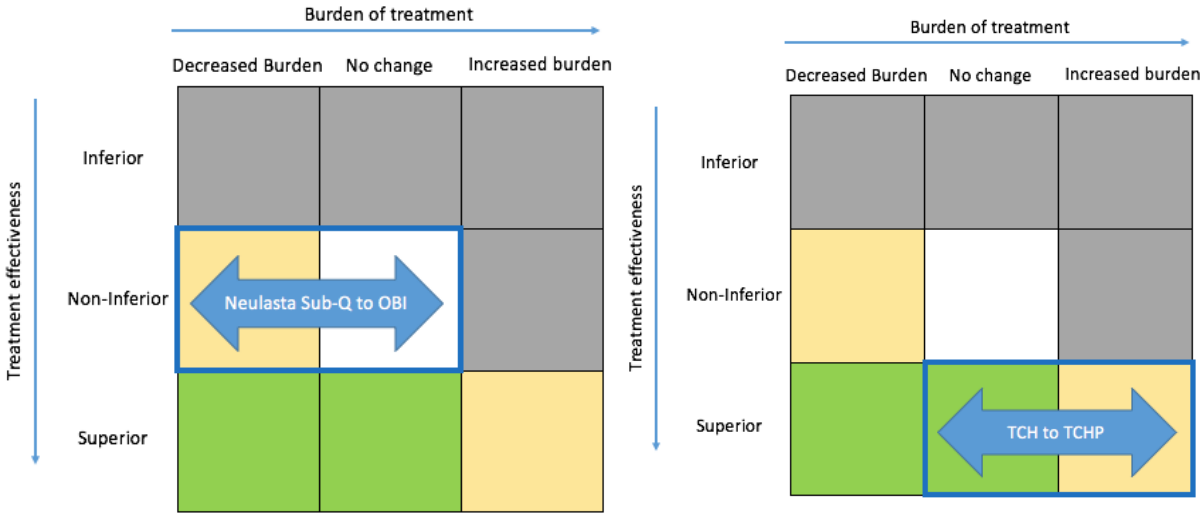
Figure 4.1. Change in treatments are desirable if they are clinically more effective and reduce the burden of treatment.

This chapter details whether quantitative measures of treatment burden are sensitive to subtle changes in chemotherapy treatment protocols. We apply our methods of quantitative measurement of treatment burden to a retrospective cohort of early stage breast cancer patients receiving neoadjuvant or adjuvant infusion drug therapy. In doing so, we demonstrate that a non-inferior therapy can decrease treatment burden, and that a therapeutically superior treatment strategy may increase treatment burden beyond expectations.

The introduction of the on-body-injector (OBI) for the granulocyte colony-stimulating factor, pegfilgrastim (Neulasta) is an example of a protocol change that is clinically non-inferior but may decrease treatment burden. Neulasta is given by subcutaneous injection 24 to 72 hours after chemotherapy to increase neutrophil production and decrease the risk of infection and febrile neutropenia(74)(75). Patients receiving Neulasta via subcutaneous injection either have to

return to the infusion clinic the day after their chemotherapy to receive the injection(76), or self-administer the injection at home. In contrast, an OBI is a device that is attached to the patient during their infusion appointment and programmed to automatically inject medication at a time specified by the provider(77).

A previous study showed that pegfilgrastim administered via OBI was clinically non-inferior to subcutaneous injection(78). The study used serum concentration over time and adverse event occurrence to determine that the two modes of Neulasta administration were equally effective. While the authors may have implied that using the OBI would decrease work patients must do, there was no empirical evidence showing that the OBI actually benefited any patients. Therefore, this clinical trial could have strengthened its conclusions about the benefit of using the OBI by showing the difference in treatment burden between patients who received Neulasta through the OBI versus those who received Neulasta through a subcutaneous injection. Starting in January 2015, the Vanderbilt Cancer Center made Neulasta OBI available in place of the subcutaneous injection, thus obviating the need for the patient to return to the infusion clinic the day after chemotherapy or complete the approval process to take the drug home. We hypothesize that patients who started a given chemotherapy regimen with the Neulasta OBI would have fewer unique appointment days compared to patients who received in-clinic subcutaneous Neulasta. If the burden of treatment is reduced, the transition to using the OBI instead of the next day subcutaneous injection is a desirable change.



Figures 4.2 and 4.3. Neulasta OBI is non-inferior to the subcutaneous injection of Neulasta but may reduce treatment burden. TCH with pertuzumab a clinically superior treatment but may increase patient burden.

The addition of pertuzumab to docetaxel, carboplatin, and trastuzumab (TCH+P) chemotherapy protocols for patients with HER2-positive breast cancer is an example of a therapeutically superior treatment that may significantly increase treatment burden. Pertuzumab is a monoclonal antibody that complements trastuzumab by inhibiting ligand-dependent signaling between HER2 and HER3, thus inhibiting cell division(79). Clinical trials for pertuzumab showed that pathological complete response increased to 66% for patients receiving neoadjuvant TCH+P(80) compared to just 39% pathological complete response in patients who received just docetaxel, carboplatin, and trastuzumab (TCH)(81).

While these clinical trials showed that the addition of pertuzumab was therapeutically superior, it increased toxicity by adding another infusion medication. The percentage of patients with decreased left ventricle ejection fraction did not differ much between TCH and TCH+P, but patients receiving TCH+P experienced an increase incidence in most grade 3 or 4 side effects compared to TCH including neutropenia, leukopenia, diarrhea, and vomiting(80)(81). Although readers can infer that grade 3 and 4 adverse events from chemotherapy toxicity would require

some follow-up care, these studies do not state the increased treatment burden for adding pertuzumab to TCH. At Vanderbilt, addition of pertuzumab to TCH chemotherapy adds about 60 minutes to the total infusion time. With the increase in toxicity related adverse events, we hypothesize that the change in time spent in clinic will increase by more than 60 minutes per cycle for patients on TCH+P versus patients on TCH. The extent of this increase could differentiate it from being merely a desirable change to an ideal change where clinical efficacy is increased without significant increase in treatment burden.

Quantitative assessments of treatment burden may inform patient and provider decisions about treatment paths and provide evidence that new treatments increase or decrease patient work. We will show how measures of treatment burden related to patient encounters were affected by the transitions from Neulasta administered via subcutaneous injection to OBI, and from TCH to TCH+P. Overall, the healthcare system should strive to minimize patient treatment burden, but at the very least we should strive to better understand the impact of our interventions on patient burden.

4.2. Methods

4.2.1. Patient cohorts

We performed a retrospective analysis of treatment burden for early stage breast cancer patients who received systemic infusion therapy in the adjuvant or neoadjuvant setting at the Vanderbilt University Medical Center (VUMC) between 2005 and 2016. Breast cancer patients were identified by the presence of a respective ICD-9 (174) or ICD-10 (C50) administrative billing code in the enterprise data warehouse. Patient chemotherapy treatment protocols were identified from the pharmacy information system using a previously developed method(82). The

Vanderbilt Institutional Review Board approved this study and granted a waiver of consent since we analyzed a large population of patients in aggregate (IRB #151003).

3.2.2. Comparing therapeutically non-inferior protocols

We compared the treatment burden of breast cancer patients receiving dose-dense doxorubicin and cyclophosphamide (ddAC) chemotherapy with Neulasta administered by one of three routes: 1) subcutaneous injection administered in the infusion center 24-72 hours after chemotherapy, 2) subcutaneous injection administered at home 24-72 hours after chemotherapy, or 3) OBI injection placed on the body in the infusion center on the same day as their chemotherapy treatment.

3.2.3. Comparing a therapeutically superior protocol

We compared the treatment burden of patients receiving docetaxel, carboplatin, and trastuzumab (TCH) versus docetaxel, carboplatin, trastusumab, and pertuzumab (TCH+P) therapy. During this same time period, the Neulasta OBI was also introduced, so we performed a sub-set analysis to evaluate any impact this might have had on detecting changes in treatment burden between TCH and TCH+P.

3.2.4. Burden of treatment measures

We used the same measures developed in chapter 2 to compare the treatment protocols. Since we are interested in the complete burden patients experience, we collected data for all types of encounters from the start of their first day of chemotherapy to one cycle length equivalent after their last cycle date.

4.3 Results

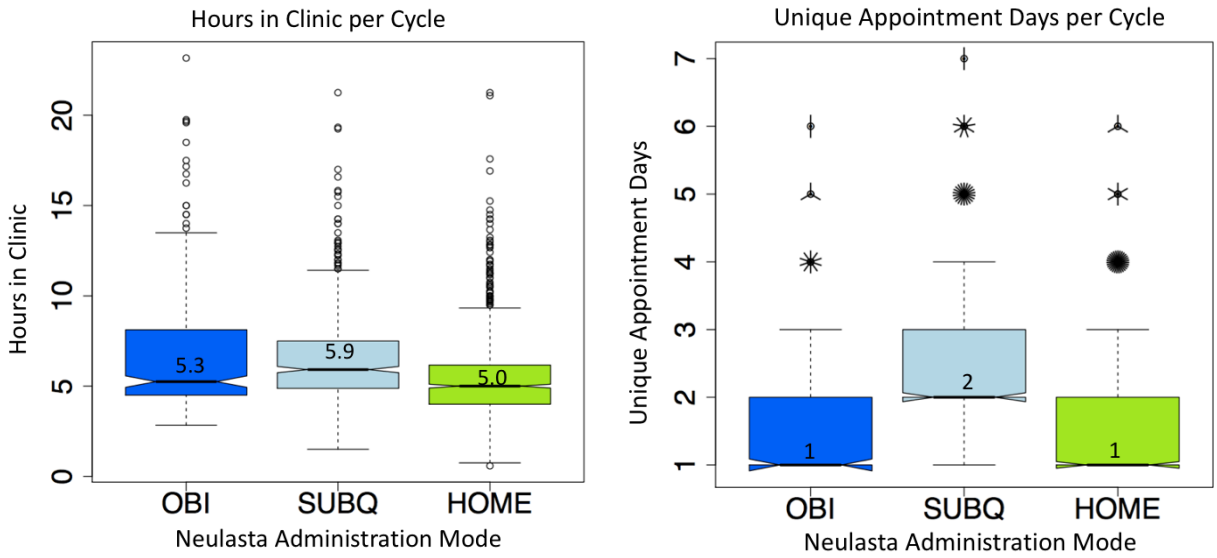
Table 4.1 compares the encounter based treatment burden measures between different modes of Neulasta administration for breast cancer patients who received ddAC. From January

2005 to September 2016, 559 patients received 1953 cycles of ddAC. Among those cycles, Vanderbilt administered 1053 doses of subcutaneous Neulasta by take-home injection, 576 next-day subcutaneous injections, and 324 OBIs. Cycles where Neulasta was administered by next-day injection had patients spending about 30 minutes longer in appointments and one additional day in clinic per cycle. While much less prominent, cycles where Neulasta was administered by take-home injection had slightly less time in clinic than cycles where the OBI was administered. Cycles where patients received the subcutaneous injection of Neulasta the next day had a higher admission rate than OBI and take-home Neulasta cycles.

Table 4.1. Summary of treatment burden for ddAC cycles by Neulasta administration. **Median** (IQR).

	OBI	Next-Day SubQ	Take-Home SubQ
Total number of cycles in group	324	576	1053
Appointment count	**4** (3-5)	**4** (4-6) *	**3** (3-4) *
Hours in appointments	**3.7** (3.6-4.6)	**4.3** (4.1-5.3) *	**3.6** (3.3-4.3) *
Hours waiting between appointments	**1.2** (.67-3.0)	**1.3** (.67-2.2)	**1.7**(.67-1.9)
Total hours in clinic	**5.3** (4.5-8.1)	**5.9** (4.9-7.5)	**5.0** (4,6.2) *
Unique appointment days	**1** (1-2)	**2** (2-3) *	**1** (1-2)
Percentage of cycles with admission	3.7%	5.9%	2.3%
Average hours length of stay per cycle	1.4	3.0	.8

* Wilcoxon p-value <.001 compared to OBI



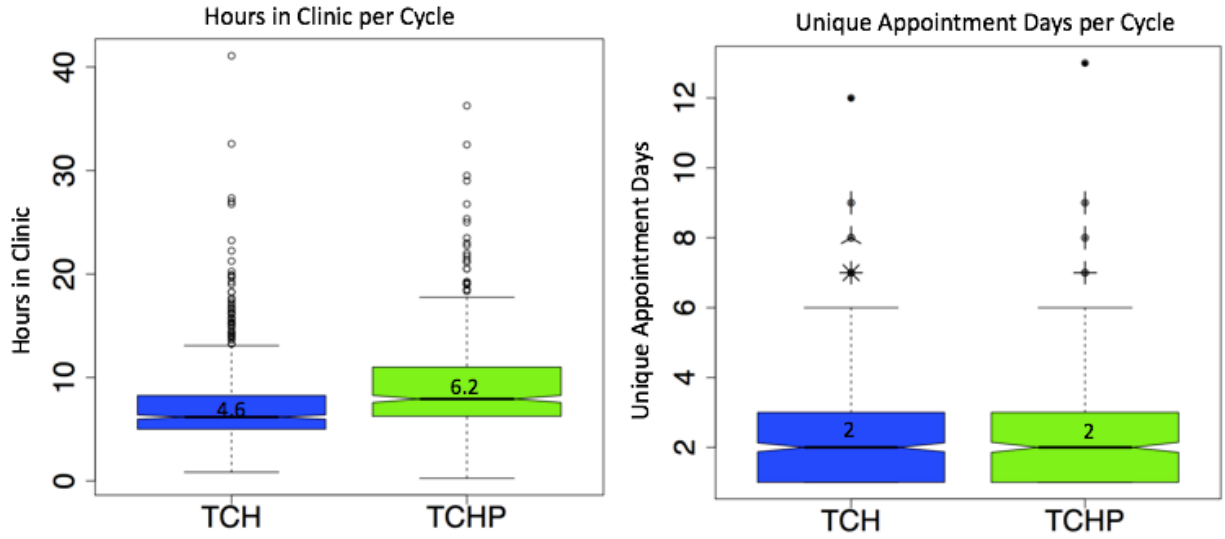
Figures 4.4 and 4.5. Hours spent in clinic and unique appointment days per cycle by Neulasta administration mode for ddAC patients. Figure 4.5 is a sunflower plot where each outlier point is one "petal" of the sunflower.

Table 4.2 compares various dimensions of quantitative treatment burden between breast cancer patients receiving TCH versus TCH+P. There were 131 patients who received TCH and 94 patients who received TCH+P from January 2008 to September 2016.

Table 4.2. Summary of treatment burden comparison between patients receiving TCH and TCH+P. **Median** (IQR).

	Overall		Next-Day SubQ		OBI	
	TCH	TCH+P	TCH	TCH+P	TCH	TCH+P
Total number of cycles in group	624	476	208	114	16	178
Appointment Count	**4** (3-6)	**4** (3-7)	**5** (4-7)	**5** (4-7)	**4** (3-9)	**4** (3-6)
Hours in appointments	**4.6** (3.6-6.1)*	**6.2** (5.1-8.4)*	**5.1** (4.4-6.5)*	**6.8** (6.1-9.0)*	**5.3** (4.6-8.9)	**5.7** (4.6-7.5)
Hours waiting between appointments	**1.4** (.92-2.4)	**1.4** (.91-2.7)	**1.5** (.91-2.8)	**1.4** (.92-2.5)	**1.0** (.60-1.8)	**1.4** (.67-3.6)
Total hours in clinic	**6.2** (5.0-8.3)*	**7.9** (6.3-11)*	**6.8** (5.5-9.3)*	**8.5** (7.3-11)*	**6.3** (5.4-9.5)	**7.8** (6.0-11.5)
Unique appointment days	**2** (1-3)*	**2** (1-3)*	**3** (2-4)	**3** (2-4)	**1.5** (1-4)	**2** (1-3)
Percentage of cycles with an admission	7.0%	1.7%	6.7%	0.9%	56%	1.1%
Average hours length of stay per cycle	2.6	1.6	3.3	0.1	8.7	.37

* Wilcoxon p-value < .001



Figures 4.6 and 4.7. Hours spent in clinic and unique appointment days per cycle for TCH and TCH+P patients.

The median cycles where the patients received TCH+P had 90 minutes more appointment time and time spent in clinic. However, there was not a noticeable increase in unique appointment days as the median cycle for TCH and TCH+P both had two unique appointment days. TCH+P had a much lower percentage of cycles where patients were admitted to the hospital. These results remained consistent when looking at patients on TCH or TCH+P who received subcutaneous Neuasta the day after chemotherapy. However, when narrowing the analysis to just cycles where the Neulasta OBI was given, results were inconclusive due to the low number of patients who had the OBI with TCH.

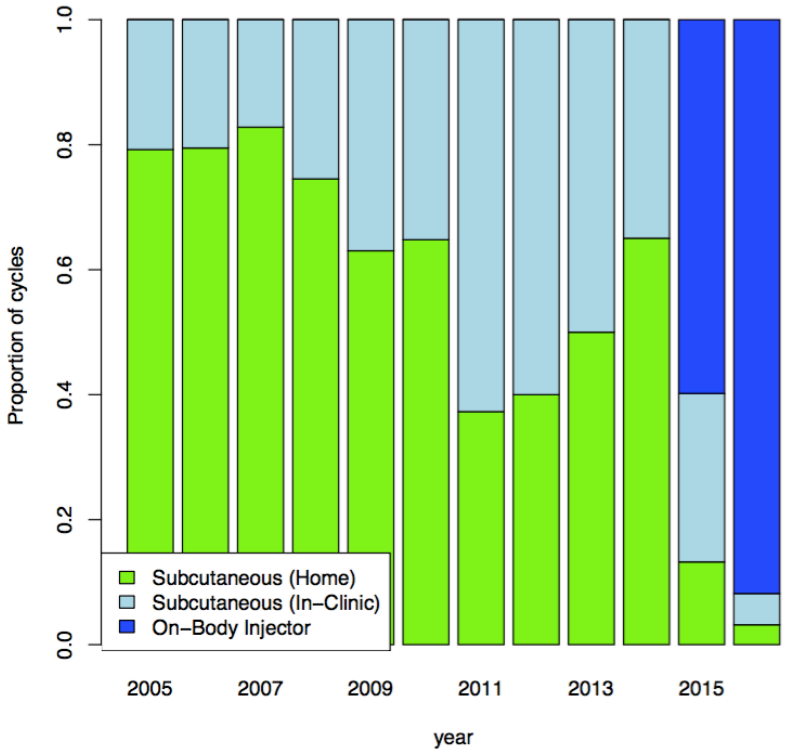


Figure 4.8. Proportions of ddAC cycles that had Neulasta administered at home, in clinic, and via OBI over time.

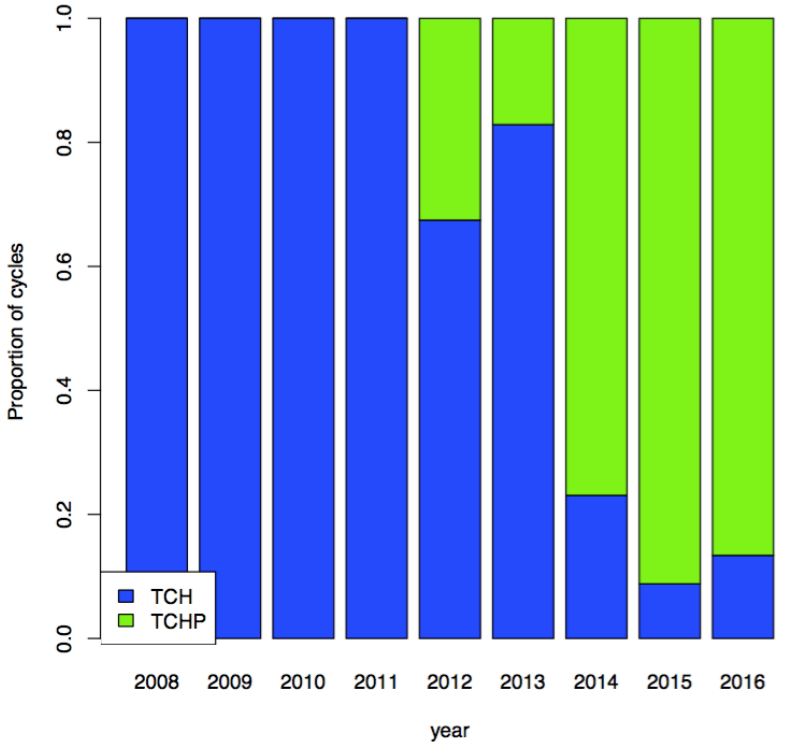


Figure 4.9. Proportion of TCH cycles that included and did not include pertuzumab over time.

The use of pertuzumab and various Neulasta administrations changed over time. With ddAC patients, we first used the OBI in January 2015 and it quickly became the most popular method of administering Neulasta. Vanderbilt first used pertuzumab with TCH in May 2012. In 2013 and after, we used TCH+P much more than TCH for HER2 positive breast cancer patients. To get a sense of how the overall burden to the patient changed after each of these changes in medical practice, table 4.3 compares the overall treatment burden aggregated by patient before and after Vanderbilt introduced the new respective treatment.

Table 4.3. Overall patient burden before and after the introduction of pertuzumab to TCH and the Neulasta OBI to ddAC. **Median** (IQR).

	ddAC		TCH/P	
	Before 1/2015	After 1/2015	Before 5/2012	After 5/2012
Total number of patients in group	441	118	72	153
Mean number of Cycles	3.5	3.6	4.9	4.9
Appointment Count	**14** (10-17)	**15** (12-19)	**26** (20-33)	**25** (19-31)
Hours in appointments	**15** (12-17)	**15** (14-18)	**25** (19-31)	**32** (21-39)
Hours waiting between appointments	**5.3** (3.0-7.4)	**5.3** (3.5-8.6)	**9.7** (6.1-13)	**9.3** (5.8-13)
Total hours in clinic	**21** (16-24)	**22** (18-28)	**35** (28-44)	**41** (32-53)
Unique appointment days	**7** (4-9)	**6** (4-8)	**12** (8-17)	**10** (7-14)
Percentage of patients with admission	15%	8%	17%	22%
Average hours length of stay	7	3	7	12

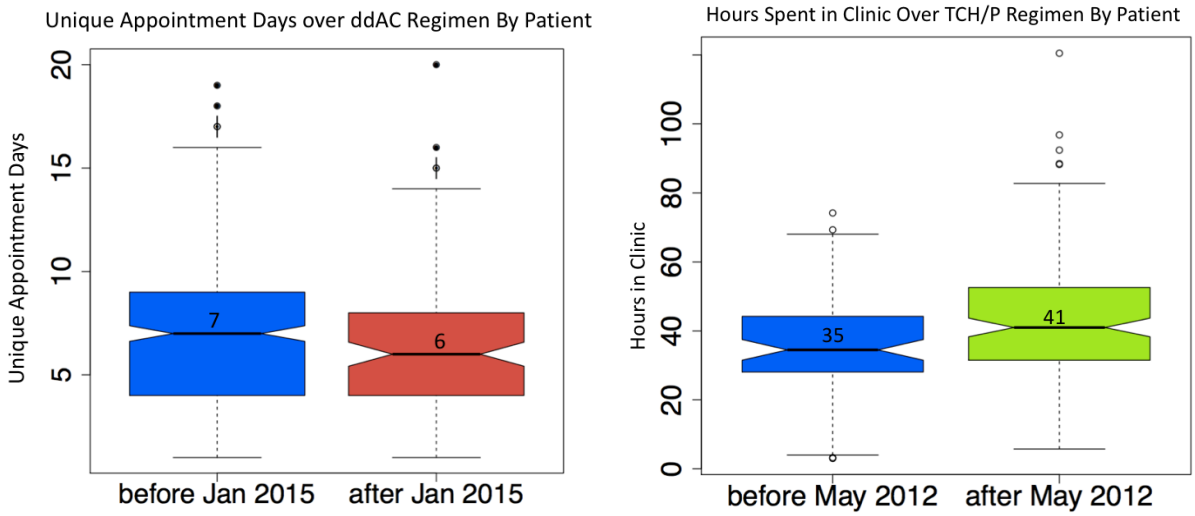


Figure 4.10. Unique appointment days across whole ddAC regimen before and after January 2015.

Figure 4.11. Total Time in clinic across whole TCH/P regimen before and after May 2012.

Patients who received ddAC after January 2015 when the OBI was introduced experienced one more fewer appointment day across their chemotherapy regimen compared to patients on ddAC before January 2015. Patients who received either TCH or TCH+P after May 2012 when TCH+P was first administered at Vanderbilt experienced six additional hours in clinic compared to those who received one of these regimens before May 2012.

4.4. Discussion

Results showed that while changes in chemotherapy treatment protocols altered burden factors, some of these changes were more nuanced. Patients receiving ddAC with Neulasta administered via OBI experienced a decrease in unique appointment days but only a small change in the total time spent in clinic. Unique appointment days for ddAC patients with Neulasta OBI had one fewer unique appointment day and about 30 minutes less appointment time per cycle. Since a next-day Neulasta injection appointment is only 30 minutes long, we did not expect to see a significant change in appointment time for OBI patients. These results show that the transition to using the OBI use is a desirable change for patients who are concerned

about unique appointment days but not as beneficial for patients who want to decrease the time spent in clinic. Patients who live far away from the chemotherapy clinic would benefit most from the OBI compared to patients who live very close to the medical center who may prefer to come into the clinic to get the Neulasta injection from a nurse. Another advantage of the OBI was that cycles where Vanderbilt used the OBI had fewer admissions than those of the next-day subcutaneous injection. This reduction in admissions could be a result of the more precise timing of the Neulasta injection by the OBI or from the decrease in stress to the patient from not having to return to the clinic.

Although the appointment metrics are similar for OBI and take-home injection patients, the OBI may provide other burden alleviating benefits. Neulasta is an expensive medication and there is an extensive authorization process that the patient must complete. Patients who take home Neulasta also have to participate in training on how to properly perform a subcutaneous injection or find a healthcare professional in their neighborhood who can help give the injection. Additionally, there may be a co-pay for taking home Neulasta that adds to the financial burden of care. OBI patients would not need to pay since applying the OBI is part of their chemotherapy encounter.

Although the OBI was effective in reducing the number of days patients have to travel to the medical center, there may be some hidden disadvantages of reducing treatment burden. Patients who return to the infusion clinic a day or two after their chemotherapy can report any adverse reactions to the nursing staff. This built-in follow-up session allows patients to get treatment for complications before they get worse. Considering that the rate of admissions and emergency room visits did not increase in OBI patients, it does not appear that there were more complications with OBI use. Nevertheless, it is important that providers consider patients that

may benefit from more visits to the clinic when deciding to prescribe burden alleviating treatments like the OBI.

The addition of pertuzumab to the TCH protocol increased the appointment time and total time for appointments by about 90 minutes per cycle but did not significantly increase the wait time or the unique appointment days. In addition to looking at TCH and TCH+P patients overall, we subsetted those patients into those receiving Neulasta subcutaneously the next day and those receiving Neulasta with the OBI, since the mode of Neulasta administration could be a confounding variable. We did not include a separate analysis of patients who received Neulasta at home since that data was not available in the medication dispensing records. There were only 10 cycles of TCH patients who received the OBI, but the 90-minute increase in appointment time and total time for TCH+P patients was true in the subset of patients receiving subcutaneous Neulasta. The finding that the addition of pertuzumab to TCH did not add unique appointment days is important for providers to communicate to their patients who may be concerned with having to make additional trips to the clinic. However, the 90-minute increase in appointment time exceeds the expected 60-minute increase from the increased infusion time. The increased appointment time without the increase in unique appointment days shows that complications due to increased toxicity of TCH+P may have been handled on days where the patient already had other appointments. Based on past evidence that TCH+P is therapeutically superior to TCH, we would conclude that adding pertuzumab to TCH is close to an ideal change for patients concerned about the work associated with unique appointment days but just a desirable change for patients concerned about the total time they spend in clinic.

One interesting finding was that the percentage of cycles where the patient was admitted was less for TCH+P than TCH, despite TCH+P having higher toxicity as discussed previously.

However, when aggregating across patients, we observed that the percentage of patients receiving TCH/P who were admitted after pertuzumab was introduced in May 2012 increased by 5%. This may imply that patients who received TCH after May 2012 were admitted more often than TCH patients before May 2012. One explanation for this is that since TCH+P is a newer treatment protocol, providers focused more intently on managing TCH+P patients than TCH patients after May 2012 resulting in a lower admission rate for TCH+P patients.

Table 4.3 shows how patient burden changed after the new treatment options were introduced. The changes aggregated by patient are less significant compared to the cycle by cycle comparison. Since we observed a reduction of one unique appointment day per cycle with the OBI compared to the next day subcutaneous injection, we would expect a reduction of three to four unique appointment days per patient after the OBI was implemented. However, the median patient who received ddAC after the OBI was introduced in January 2015 experienced only one fewer unique appointment day over the course of their chemotherapy regimen. There are several explanations for the diminished effect. Patients of a given protocol may have undergone differing numbers of cycles. Additionally, a patient may have Neulasta administered via more than one mode from cycle to cycle. While Neulasta OBI use overtook subcutaneous Neulasta quickly, there were still a significant number of cycles after the implementation of the new treatment that would have diluted the effect on treatment burden. Furthermore, figure 4.5 shows that unique appointment days had a long tail on the upward side meaning there were more outliers of cycles where patients experienced a high number of unique appointment days. Patients receiving ddAC after the OBI was implemented with a cycle that included any of these outliers may not have realized the benefit of the OBI in reducing overall unique appointment

days across their chemotherapy regimen. The elimination of the next-day infusion would have had a small impact on the overall burden for these patients.

The median TCH/P patient experienced six more hours in clinic after Vanderbilt introduced pertuzumab in May 2012. With the observed 90-minute increase per cycle, we would expect an increase of 7.5 hours per patient after the first TCH+P administration in May 2012. The six hour increase in total time spent in clinic is less than the 7.5 hours expected from the per cycle data but still greater than the five hour increase we expect from just added infusion time from adding pertuzumab. The six hour increase further supports the hypothesis that increased toxicity from pertuzumab may cause patients get more care to address adverse events from their chemotherapy.

4.5 Conclusions

In this chapter, we demonstrated treatment burden changes with changes in chemotherapy protocols. In our study population, adding pertuzumab to TCH increased the appointment time by more than the 60 minutes of increased infusion time, indicating that the increased toxicity led to more complications. Due to its therapeutic superiority, the increase in treatment burden made the transition from TCH to TCH+P a desirable but not an ideal change. For ddAC patients, unique appointment days decreased when VUMC used the OBI showing that the new technology succeeded in its goal to reduce treatment burden.

CHAPTER 5

Conclusions and Future Work

5.1 Conclusions

Through this study, we sought to introduce the concept of patient burden to the medical oncology and informatics communities. We succeeded in developing several measures for treatment burden computed from clinical encounter data at Vanderbilt. We applied these measures to a population of breast cancer patients and were able to differentiate burden of treatment in patients with stage I-III breast cancer. In this population, we observed patterns of treatment over time after date of diagnosis. We also used these measures to detect changes in burden with adjustments in chemotherapy protocols, revealing that devices designed to decrease burden had their intended effect, and that chemotherapy drugs that were highly toxic, while therapeutically superior, added to patient burden.

Therefore, with the measures we developed in this study, we demonstrate a framework for three new studies of treatment burden. The first type of study from Chapter 3 is to visualize the distribution of treatment burden in a population of patients and to identify outliers who may require additional attention. The second type of study, also from Chapter 3, is to track the change over time in treatment burden for a patient or population of patients in order to educate patients about the impending work associated with their condition, or for healthcare organizations to allocate resources required to address future demand. The third type of study from Chapter 4 compares treatment burden before and after the implementation of an operational or clinical practice change. Healthcare organizations and private companies should perform these studies to determine the extent to which new treatments increase or decrease burden.

5.2 Future Work

Future work includes incorporating additional factors that influence patient burden identified in previous literature. To more accurately capture the patient experience related to appointments, we plan to incorporate commute time into their burden assessment by adding the time to drive from their home address to the clinic address before and after appointments. We will use other structured data such as medication prescriptions to determine the frequency of home medication use, and billing information to approximate other medical encounters not captured directly as appointments. There is also potential for natural language processing of notes to capture other provider recommended activities crucial to outcomes such as exercise or diet changes. Complementary to the need for an accurate assessment of a patient's treatment burden is the determination of a patient's capacity for treatment. With burden and capacity, we can compare outcomes for patients for whom burden exceeds capacity against those who receive care within their means.

To extend our work tracking burden with changes in healthcare practice, we plan to investigate whether changing from a fee-for-service payment model to a value-based or bundled payment model decreases treatment burden. As hypothesized in the introduction, we anticipate that incentivizing healthcare systems to decrease costs should result in a decrease in treatment burden for patients. The Oncology Care Model program where the Centers for Medicare and Medicaid Services (CMS) pays healthcare systems based on episodes of care may present an opportunity to make those comparisons in patients with cancer(83).

We also want to use qualitative methods such as surveys and patient interviews to correlate our quantitative measures with patient and caregiver experiences of burden. We plan to perform interviews with patients themselves as well as cancer navigators who are healthcare

professionals familiar with struggles cancer patients face(84). We also want to present patients, providers, and support staff with treatment burden information through electronic media or decision support. Observing how members of the healthcare community use this information to improve patient care will ultimately determine its impact to society. By better understanding burden of treatment, we can begin to deliver precision medicine not only based on genetic makeup and disease phenotypes, but also on the patient's capacity to comply with treatment plans in order to maximize the likelihood for improved outcomes.

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