Delivering the Right Amount of Care – Sometimes Less Is More

Delivering the Right Amount of Care – Sometimes Less is More

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Dissertation Introduction

New technologies utilized in clinical practice offer improved tools for diagnosing and treating patients. In some cases, these improvements cause unintended consequences by leading to the diagnosis of indolent or otherwise clinically-irrelevant disease. In my first two chapters, I examine technological advances in screening and diagnosis that have led to questions regarding whether it is necessary to treat disease at as early a stage as it is possible to diagnose it. I conduct cost-effectiveness analyses to determine whether application of less-intensive clinical regimens leads to better and more cost-effective outcomes for patients with thyroid and prostate cancer. In these two cases I find that less intensive therapeutic options provide better results. In my third chapter, I use electronic medical records data to examine a case where old technology is sufficient to identify disease at a stage suitable for the application of well-established and highly efficacious treatments. In contrast with thyroid and prostate cancer, I find that a significant proportion of patients eligible for hypertension treatment are not treated,

despite simple criteria for diagnosis, low-cost therapies and clear recommendations for their use within well-established and accepted guidelines.

In Chapter One, I evaluate prostate cancer, a disease which is expected to be diagnosed in approximately 161,000 men in the United States in 2017, making it the third most frequently diagnosed cancer. In the early 1990s, rates of prostate cancer diagnoses in the United States increased dramatically due to broader use and widespread adoption of the prostate-specific antigen (PSA) test. Although these diagnosis rates peaked in the mid-1990s, today, rates remain elevated by about 50% compared to pre-PSA-testing levels. Despite this, mortality rates have remained nearly constant, suggesting that many patients identified through PSA screening may represent "over-diagnosed" or “over-treated” patients. Over the past 15 - 20 years clinicians have developed and tested less intensive, yet highly effective Active Surveillance treatment regimens. These regimens offer patients who satisfy a very specific set of criteria an option to delay immediate radical treatment, thereby avoiding the morbidities that are associated with surgery, chemotherapy or radiation therapy. Several variations of Active Surveillance have been practiced in different centers around the world, but there is no clear consensus regarding which is best, and for which patients. In my first chapter I undertake a systematic literature review to identify variants of Active Surveillance, identifying three frequently reported variations representing a high, medium and low-intensity protocol. I then undertake a decision analysis to

compare these to the existing radical treatment mix that is practiced in the US. I find that Active Surveillance of medium intensity utilizing biopsy intervals of between 18 – 24 months is the most efficient option. It allows men with low-risk prostate cancer to achieve an additional 217 quality-adjusted life days at an incremental cost of just over $2,000, making it a highly cost-effective strategy. I also find that a modified version of this protocol using biopsies at ≥ 3 year intervals is more efficient, but may be less desirable to clinicians due to its longer period between surveillance biopsies and its lack of widespread clinical use.

In Chapter Two, I examine thyroid cancer. Similarly to prostate cancer, diagnoses of thyroid cancer have increased dramatically in the past 15 years, yet mortality has remained low and nearly constant. In this chapter I conduct a cost-effectiveness analysis focusing on treatment for patients with papillary thyroid carcinoma, a subtype of thyroid cancer that accounts for approximately 85% of the nearly 56,000 incident cases expected in 2017 in the United States. In the most recent (2015) update to the American Thyroid Association (ATA) *"Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer"*, the ATA recommended two major changes to their 2009 guidelines. First, that patients with specific tumor characteristics could be treated with lobectomy, a less intensive surgery than the prevailing surgery, total thyroidectomy. Second, for patients with specific nodule/tumor characteristics, Active Surveillance of their cancer via annual ultrasound

imaging was a viable option. For my second chapter, I created a Markov microsimulation model to determine whether these major changes to the guidelines improved outcomes, decreased costs, or both, for patients with papillary thyroid carcinoma. I find that the 2015 guidelines represent a dominant treatment strategy compared to the strategy recommended in the 2009 guidelines. Even after allowing for uncertainty via deterministic and probabilistic sensitivity analysis the 2015 strategy remains dominant, or at worst, highly cost-effective in expectation.

In my third chapter, I utilize a national electronic medical records database to evaluate physicians' behavior regarding rates of prescription for pharmacologic therapies to treat hypertension. Unlike prostate cancer and thyroid cancer where chapters 1 and 2 indicate that there is overtreatment, hypertension presents a contradictory case where there appears to be significant undertreatment. In 2003, the *"Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure"* issued its 7th revision of the guidelines for the diagnosis and treatment of hypertension (JNC7). Within these guidelines, the JNC provided clear blood pressure thresholds of 140mmHg systolic and 90mmHg diastolic for the initiation of hypertension treatment and specified appropriate pharmacologic therapies. I utilized electronic medical records data from approximately 50 million patients during 2010 - 2013 from across the United States. Using these data, I determine how often pharmacologic treatment was consistent with that which would be expected if the

recommendations of the JNC7 guidelines were followed for those patients. I find that the majority of patients meeting the JNC7 systolic and diastolic blood pressure criteria for treatment do not receive a prescription as recommended by the JNC7 guidelines. Secondarily, the rates of treatment and guideline concordance vary by age, race, and sex. Through the use of logistic regression analysis I determine that patients satisfying the JNC7 criteria for systolic blood pressure have odds of treatment of 2.98 compared to those who do not, but that for patients with systolic blood pressure readings near the threshold of 140mmHg the odds of treatment for those who satisfy the JNC7 criteria increase to 7.75. From these results, I infer that the JNC7 guidelines successfully stimulate treatment of patients who satisfy the criteria defined in the JNC7, but that there is still significant undertreatment of eligible patients.

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Finally, to my committee; Milt, Richard, Joe and Scott. Your feedback and support throughout the process has been wonderful. I look forward to many more years of collaboration.

Chapter 1

A Decision Analysis Comparing Three Active Surveillance Protocols for the Treatment of Low-Risk Prostate Cancer

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Abstract

Introduction

Active surveillance (AS) is a viable prostate cancer management option for 80% of newly diagnosed men[1] No direct comparison between different variants of AS protocols has been conducted[2–4]. We developed a model to evaluate which protocol is optimal for men with low-risk prostate cancer.

Methods

We conducted a decision analysis using a microsimulation model. Men diagnosed with low-risk prostate cancer at age 65 were modeled as having been treated with either immediate curative therapy or via any of three AS protocols. Modeled AS protocols represent those in the literature; a modified AS protocol was included in a sensitivity analysis. Immediate curative therapy includes radical prostatectomy, external beam radiation therapy, or brachytherapy. Outcome measures were quality-adjusted life years (QALYs) and treatment costs.

Results

Immediate curative therapy produced fewer QALYs than all variants of AS. Of the AS protocols evaluated, biennial biopsy was the only efficient option and had an incremental cost-effectiveness ratio of $3,490/QALY relative to immediate therapy. It delayed the need for curative therapy by mean time 56 months. In probabilistic sensitivity analysis, it was preferred in >86.9% of cases. A modified version of low-intensity AS dominated all other options.

Discussion

For a 65-year-old man with low-risk prostate cancer, active surveillance with biennial biopsy is highly cost-effective compared to immediate treatment or commonly reported alternative AS protocols. An AS protocol using triennial biopsy dominates all other strategies and should be investigated as an alternative. The optimal choice of AS strategy depends on patients' tolerance for periodic biopsies; physicians should therefore incorporate patient preferences into decision-making.

Manuscript

Introduction

In the early 1990's, the advent of prostate-specific antigen (PSA) screening led to increased detection and diagnosis of prostate cancer.[5] Early-stage cancers, which often have a more indolent clinical course, comprise the most significant component of this increase in incidence.[6–18] Approximately 80% of newly diagnosed patients today are found to have low-risk, early stage prostate cancer, a term generally reserved for organ-confined disease (T1 or T2a), a PSA < 10 and a Gleason Score of six or less on prostate biopsy.[1,19–23] In response to this increased incidence of low-risk cancers, clinicians have developed less aggressive management algorithms.[24–26] Traditional therapies such as radical prostatectomy, brachytherapy and external beam radiation therapy frequently lead to side effects such as erectile dysfunction and urinary and bowel incontinence, whose risk may outweigh the benefits of immediate treatment. Despite the increased utilization of less aggressive strategies, no definitive protocol exists.[2,4,27]

For men initially diagnosed with low-risk disease, as is usually discovered via screening, the rate of progression is often slow enough that the side effects of radical treatment can be delayed and in some cases, avoided, without reducing the patient's survival.[28–32] The term "Active Surveillance" implies a treatment plan whereby (A) the overall intention of treatment, if it occurs, is to cure the patient (as opposed to watchful waiting where the intention is palliative), (B) the rate of progression of the cancer is slow

enough that a curative radical treatment can be initiated at a later point in time if needed, and (C) radical treatment may be permanently avoided because the cancer's rate of progression is slow enough that even patients with life expectancy of >10 years may die of other causes.[33–37]

Table 1.1. Existing Studies Reporting AS Protocols and their Eligibility Criteria

Institution	Stage	GS	PSA	PSAD[1]	Positive Cores	Cancer/ Core
Johns Hopkins	1c	≤6		≤0.15	≤2	≤50%
Miami	≤T2a	≤6	≤10		≤2	≤20%
Aarau, Switzerland		≤6		≤ 0.15	≤2	≤50%
McGill	<2b	≤6			≤2	≤50%
UCSF	≤2	≤6	≤10		≤33%	≤20%
Dana-Farber	1c-2c	≤6			<3	≤50%
Chicago / MSKCC[2] /	1-2a	≤6	≤10		≤3	
Royal Marsden	1-2	≤6[3]	≤15		≤50%	
Cleveland Clinic	1c-2a	≤6	<10			
Princess Margaret	1c-2a	≤6	≤10		≤3	≤50%
MSKCC	≤2a	≤6	≤10		≤3	≤50%
Monash & Southern		≤7	6.5[4]		≤2	
PRIAS	1c-2	≤6	≤10	≤ 0.2	≤2	
Toronto	1	≤6[5]	≤10[6]			
Connecticut	1-2a	≤6	≤10		≤2	<50%

[1] In ng/ml/ml
[2] Memorial Sloan Kettering Cancer Center
[3] For patients over 65 years this was relaxed to ≤7
[4] This study did not provide a threshold. The number reported is a median Gleason sum
[5] Until January 2000, for patients over 70 years this was relaxed to ≤7
[6] Until January 2000, for patients over 70 years this was relaxed to ≤15

Active Surveillance Protocols

Historically, the approach clinicians used when monitoring patients with prostate cancer was “Watchful Waiting” (WW). In WW the overall goal is to maximize quality of life symptomatically: therefore, the protocols used for monitoring patients were low intensity, and clinical intervention was stimulated by symptoms. Under WW, the patient’s life expectancy is often predicted to be less than the life expectancy with radical treatment, but radical treatment is forgone to preserve quality-of-life.[38–41] In contrast, “Active Surveillance” (AS) protocols are more intense, since the management plan has curative intent. Over the past twenty years, different groups have used reasonable but arbitrarily set protocols to actively monitor low-risk prostate cancer patients, mainly drawing on monitoring regimens used in other fields in medicine and their own comfort levels.[31,41–55] To date, no published literature has compared multiple active surveillance protocols.

There is a wide range of intensity in the monitoring regimens of AS protocols. They range from digital rectal examination (DRE) and prostate-specific antigen (PSA) measurements every 3 months with yearly biopsies, to semi-annual DRE and PSA with biopsies every 3 to 4 years (Table 1.1).[29,42,44,48–51,54,56–63] Although the overall goal of all active surveillance protocols is to cure patients, more intense monitoring may not necessarily confer a survival advantage for patients, since it brings its own set of problems such as lower compliance and risk of protocol abandonment, and imposes burdens of patient pain and suffering, and emotional and financial costs.[64–71]

Concerns over disease progression.

Several studies of low-risk prostate cancer patients indicate that the risk of metastasis is low for a significant period of time, and that prostate cancer-specific survival rates are high for disease that has not yet metastasized.[41,72–75]

There may never be a prospective randomized trial comparing the effectiveness of various active surveillance protocols; however, we now have sufficient data to draw preliminary conclusions on what might be the optimal monitoring intensity for low-risk prostate cancer patients. We reviewed reported AS protocols and grouped them into three categories. We then modeled their clinical- and cost-effectiveness to make appropriate monitoring intensity recommendations that balance oncologic outcomes against patient mortality, morbidity and cost.

Literature Review.

We conducted a search for studies describing treatment protocols using the terms “prostate cancer” and “active surveillance” or “conservative management” or “watchful waiting“ or “expectant management”. After reviewing abstracts for relevance, our search uncovered fifty studies describing AS protocols applied to fifteen unique cohorts. We classified these studies as high-, medium- or low-intensity based primarily upon biopsy frequency.

Table 1.2: Study Protocols and Intensity Classification (H/M/L)

Institution	PSA	DRE	Biopsy	Intensity Classification
Johns Hopkins	q6	q6	q12	High
Miami	q3	q3	q12	High

Aarau, Switzerland	q6	q6	q12	High
McGill	q3	q3	q12	High
UCSF	q3-6	q3-6	q12-24	Medium
Dana Farber	q6	q6	q12-18	Medium
Chicago / MSKCC	q6-12	q6-12	q12-36	Medium
Royal Marsden	q3-6	q3-6	q18-24	Medium
Cleveland Clinic	q6-12		q24[1]	Medium
Princess Margaret	q3-6	q6	q24-36[1]	Low
MSKCC	q6	q6	q24-36[1]	Low
Monash & Southern	q3	q6	q36[1]	Low
PRIAS	q3-6[1]	q3-6[1]	q36[1]	Low
Toronto	q3-6[1]		q36-48[1]	Low
Connecticut	q6m	q6-12	q24[1]	Low

Studies considered for outcomes analysis had to provide details about three major parameters; (A) inclusion criteria used for patients to be admissible and remain under active surveillance, (B) the protocol used while patients are on active surveillance and (C) the follow-up period and oncologic outcomes such as recurrence and survival data. Recent review articles were also included, and their cited studies were incorporated into our review. Only studies performed on patients with a “curative intent” were retained (Table 1.2).

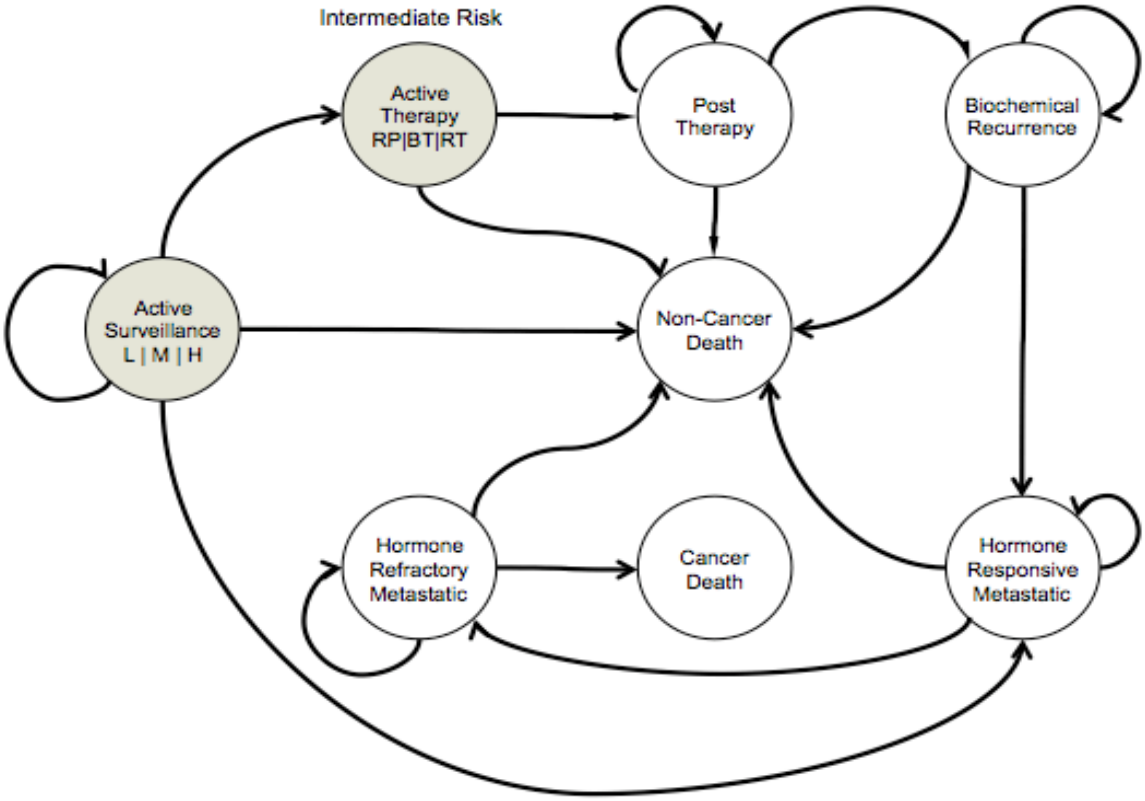
We also conducted a systematic search for economic analyses for the period December 2003 – December 2014[7]. This search identified two hundred and thirty-five studies. Sixty-one were deemed relevant. (Appendix 1).

[7] The full terms for this search are available.

Methods

We created a Markov state-transition patient-level microsimulation model with a monthly cycle length in TreeAge Pro 2015, version 15.1.0.0-v20150223 to model the effects of alternative strategies for treating low-risk prostate cancer (PSA ≤ 10ng/ml, Gleason sum ≤ 7). All other statistical analyses were undertaken in R ver. 3.1.1. A model schematic is shown in Figure 1.1.

Figure 1.1: Markov Decision Model Schematic



In the base-case analysis we simulated three variants of AS protocols, each of which resembles a protocol that has been reported on in published literature, as well as a nationally representative immediate curative treatment strategy. In the model, men are diagnosed at age 65 years, and outcomes from each of the strategies are simulated. Each man enters the model with a PSA level and PSA velocity randomly assigned from within a plausible range as identified in the literature. Men are then tracked until death from cancer or background causes. We used US Social Security Administration 2009 life tables to model background mortality risk, and discounted utilities and costs at a 3% annual rate. To reflect parameter uncertainty, we ran our model 1,000 times, each one with 10,000 patients using a unique parameter set sampled from the distributions defined. We averaged over all simulations to determine mean effectiveness and cost for each strategy. For each strategy, total QALYs and total costs per patient are reported. We performed probabilistic sensitivity analyses based on the distribution of costs and QALYs across the 1,000 randomly selected parameter sets.

Active Surveillance Protocols

Each variant of AS modeled involves DRE, PSA and Biopsy. Low-intensity AS includes DRE and PSA testing quarterly for twenty-four months, then semi-annually thereafter; confirmatory biopsy at twelve months and then triennially thereafter; and bone scans for any man whose PSA increases to a level greater than 20ng/ml. This protocol models the one used in the PRIAS study. Medium-intensity AS includes PSA and DRE testing semi-annually and biopsy biennially. High-intensity involves PSA and

DRE testing semi-annually, and biopsy annually. Table 1.2 lists the bases for each of these intensity classifications.

In an additional analysis we included a fourth AS protocol, which is a modified version of the low-intensity protocol. Unlike the low-intensity protocol modeled on PRIAS, which utilizes a confirmatory biopsy at 12 months after diagnosis, the modified low-intensity protocol does not require its first (post-diagnosis) biopsy until the third year of monitoring. It also specifies semi-annual DRE and PSA, rather than quarterly DRE and PSA for the first two years as specified in the low-intensity protocol. This protocol is not commonly practiced but may be of interest to physicians seeking a low-intensity monitoring regimen for their patients.

Any man under surveillance who no longer satisfies the eligibility criteria for any AS protocol is treated with a brachytherapy regimen identical to that in the immediate treatment strategy. We use modified probabilities for these men due to the fact that men no longer eligible for AS have a greater chance of having progressed to an intermediate disease classification. For the purposes of our analysis we did not consider the use of endorectal coil MRI, as it is not part of the standard of care of published AS protocols.

Immediate Treatment

Our immediate treatment strategy applies the age-specific nationally representative distribution of radical prostatectomy (RP), external beam radiation therapy (EBRT) and brachytherapy (BT).[76] We excluded strategies for primary androgen

deprivation therapy and cryotherapy due to their infrequent use as first-line treatment options in low-risk patients and data limitations.

Table 1.3: Model Parameters

Probabilities	Value	Distribution (SD)	Source
BCR – Intermediate-Risk	0.0453		84–87
BCR – Low-Risk Brachytherapy	0.0159		20,85
BCR – Low-Risk Prostatectomy	0.0230		20,84,88
BCR – Low-Risk Radiation Therapy	0.0230		20
Metastases During BCR	0.050 (0.01)	Beta	74,84,89
Metastases While Under AS	0.00138 (0.000037)	Beta	41,72–75,89–91
Death Due to Prostatectomy Surgery	0.00383 (0.000018)	Beta	92–94
Refractory Metastases	0.28		95
Complications due to Biopsy (Major)	0.009		66,71,80
Complications due to Biopsy (Minor)	Varies	Table	80
Long Term GI Adverse Events Brachytherapy	0.04		89
Long Term Sexual Adverse Events Brachytherapy	0.323		89,95
Long Term Urinary Adverse Events Brachytherapy	0.167		89,90,95
Long Term GI Adverse Events Prostatectomy	0.00		89
Long Term Sexual Adverse Events Prostatectomy	0.453		89
Long Term Urinary Adverse Events Prostatectomy	0.127		89,94
Long Term GI Adverse Events – Radiation Therapy	0.066		89
Long Term Sexual Adverse Events Radiation Therapy	0.48		89
Long Term Urinary Adverse Events Radiation Therapy	0.134		89
Exit Protocol due to Anxiety or Psychological reasons	0[8]		
Utilities			
Age Specific Baseline Utility	Varies	Table	96
Utility for Active Surveillance	0.817 (0.0484)	Beta	77–79
Utility while in BCR	0.731 (0.030)	Beta	77,85,89
One Time Disutility from Prostate Biopsy	-0.00274		97
One Time Disutility from biopsy complications	-0.003		66,97
One Time Disutility from Prostatectomy	-0.0959		97
Metastatic Prostate Cancer	0.364 (0.067)	Beta	77,78,90,98
GI Complications	0.74 (0.1982)	Beta	77
Sexual Complications	0.831 (0.0614)	Beta	77,79,89,98
Sexual and GI Complications	0.706 (0.0888)	Beta	77,79,90,98
Urinary Complications	0.860 (0.286)	Beta	77,89,98
Urinary and GI Complications	0.743 (0.059)	Beta	77,89,98
Urinary and Sexual Complications	0.825 (0.032)	Beta	77,89,98
Urinary, Sexual and GI Complications	0.516 (0.081)	Beta	77,89,98
Costs			
Treatment of Biochemical Recurrence	$2,565		85
Prostate Biopsy	$2,557		99
Complications of Biopsy (Major)	$13,479 ($11,800)	LogNormal	81
Complications of Biopsy (Minor)	$122		99,100
Brachytherapy	$12,600 ($7,360)	LogNormal	81

[8] We chose to use 0 for this parameter in our base case to model a situation in which patients remain on Active Surveillance protocol as long as they are eligible. We tested the robustness of our results by undertaking sensitivity analysis on this parameter over a range of plausible values.

Prostatectomy	$12,141 ($5,391)	LogNormal	81,101,102
Radiation Therapy	$20,607 ($4,544)	LogNormal	76,85,86,90,102,103
Follow Up Office Visit	$122		99
Long Term Bowel Complications (initial Costs)	$810.61		90
Long Term Urinary Complications (initial Costs)	$741.45		90
Long Term Sexual Complications (initial Costs)	$831.49		89
Treatment of Metastatic Hormone Refractory PC	$2,212		85
Treatment of Metastatic Hormone Responsive PC	$3,172		85

Men undergoing treatment may incur morbidities related to bowel, urinary, or sexual function. After treatment, patients continue in a “post-treatment” state until death from other causes, or until biochemical recurrence (BCR). While in the post-treatment state, men are monitored via PSA testing and DRE annually. If BCR occurs, men are presumed to have hormone responsive disease and are treated with hormone therapy until they become refractory and develop metastases. Men with refractory metastases are treated palliatively until death.

Model Parameters (Table 1.3)

Probabilities

All probabilities were estimated from secondary sources. Where possible multiple values for the same parameter were aggregated via random-effects meta-analysis (Appendix 1). Where data were insufficient to do this, we either used the mean and variance of the set of data to parameterize a beta distribution, or we fit the lowest and highest values as the 5%-95% range in a beta distribution.

Probabilities for frequency of metastases while in an AS protocol varied. For this parameter we performed statistical survival analysis. Using data from several studies

we generated multiple beta distributions that fit the data.[76] We then used these parameter sets to generate a beta distribution that would identify the probability at any given time point for this parameter.

We included a parameter in the model to represent the probability that patients drop out from AS protocol due to anxiety or other reasons. The base case model used a value of zero for this probability, but literature on the appropriate value for this parameter is inconclusive. Given this uncertainty, we conducted deterministic sensitivity analysis on the parameter.

Utilities[9]

Utilities were estimated for all complications and all health states. For being on any of the active surveillance protocols we used a value of 0.817 (based on a pooled estimate of several studies).[77–79] We modeled health-state utilities as beta distributions to allow for patient-level variability of preferences in the population. For transient procedure-related disutilities we applied a fixed utility decrement to each patient's current utility in each model cycle for the duration of the procedure.

Costs

Costs were determined from the published literature, the CMS Fee Schedule, the fee schedule at a major academic hospital, and AHRQ's HCUP database. We used cost analyses by prior authors for selected costs, such as costs of complications due to

[9] Utilities are numerical values, ranging from 0 (death), to 1 (perfect health) used to indicate preferences for a given health state. The summation of each year, multiplied by its utility weight is used to determine total quality adjusted life years (QALYs).

treatment. For costs associated with BT, RP and RT, we modeled a lognormal distribution to represent the possibility of a small group of high-cost patients. We fit distributions based upon either median and mean hospital costs as reported in HCUP, or in the case of RT, we used a plausible range to represent a 5%-95% confidence interval for a lognormal distribution.

Complications

Recent literature indicates that repeated prostate biopsies produce an increasing rate of complications. We used these data to create a tabular distribution on this parameter as a function of the number of biopsies (see Supplementary Table 1.1).[80] Major complications of biopsy can lead to hospitalization. We modeled costs to account for this based on our own analysis of the AHRQ HCUPNet dataset for hospitalizations associated with ICD-9-CM procedure code 60.11.[66,80,81]

We modeled the frequency of complications due to each of the treatments as both short-term and long-term adverse effects. We presumed short-term adverse effects persist for three months, and long-term adverse effects persist for the patient's lifetime.

Table 1.4: Base Case Analysis – Selected Key Results Generated By The Model for 65-yo Men with Low-Risk Disease

Outcome	Immediate Treatment	Low-Intensity Active Surveillance	Medium-Intensity Active Surveillance	High-Intensity Active Surveillance
Lifetime Metastases	10.94%	7.98%	6.30%	6.64%
Prostate Cancer Death	7.56%	6.97%	5.48%	5.70%
ATFS*	0 Months	52.73 months	56.16 months	54.91 months
Life Expectancy - Years (SD)	81.87 (0.08)	81.97 (0.15)	82.08 (0.15)	82.07 (0.15)

Results

Base Case

In the cohort of men diagnosed at age 65, medium-intensity AS was the most effective strategy, yielding 10.169 QALYs. This was followed by high-intensity AS (10.137), and then low-intensity AS (10.053). Immediate curative treatment offered the fewest QALYs (9.574), but at a lower cost ($22,988) than any of the active surveillance strategies. Among active surveillance strategies, medium-intensity AS had the lowest cost ($25,065]) and also yielded the most QALYs. The lifetime risk of developing metastatic cancer was 6.64%, 6.30%, 7.98% and 10.94% respectively for high-intensity AS, medium-intensity AS, low-intensity AS, and immediate treatment (Table 1.4). Lifetime risk of Prostate Cancer death was 5.70%, 5.48%, 6.97% and 7.56%**.**We find medium-intensity AS to be a highly cost-effective strategy, with an incremental cost-effectiveness ratio of $3,490 per QALY (Table 1.5).

Table 1.5: Base Case Analysis – Results for 65-yo Men with Low-Risk Disease

Protocol	Cost	QALY	ICER ($/QALY)	Dominance
Immediate Treatment	22,988	9.574	-	-
Low-intensity AS	~~24,890~~	~~10.053~~	-	Extended
Medium-intensity AS	25,065	10.169	3,490	None
High-intensity AS	36,638	10.137	-	Absolute

Note: Costs and QALYs discounted at 3% p.a.

Sensitivity Analysis

In probabilistic sensitivity analysis, medium-intensity AS had an 86.9% probability of being the most cost-effective strategy at a willingness to pay (WTP) criterion of $50,000/QALY. Considering cost minimization only (WTP of $0/QALY) immediate treatment is preferred with near certainty.

For parameters for which we expected model sensitivity, such as frequency of metastases, utility for being in an AS protocol, or departure from protocol due to anxiety, we undertook one-way sensitivity analyses to determine threshold values. We found the model results insensitive to changes in anxiety dropout rates for all possible values. Medium-intensity AS was the most cost-effective option for values of the utility for active surveillance greater than 0.75. (Figure 2.2(B)). For any values of metastases within 99.97% of the modeled distribution of expected probabilities of metastases while under surveillance, (i.e. <0.104% per month, a value more than seven-fold higher than best existing estimates for rate of metastases while under surveillance), medium-intensity AS was still a cost-effective strategy at WTP of $150,000/QALY. (Figure 2.2(A)).

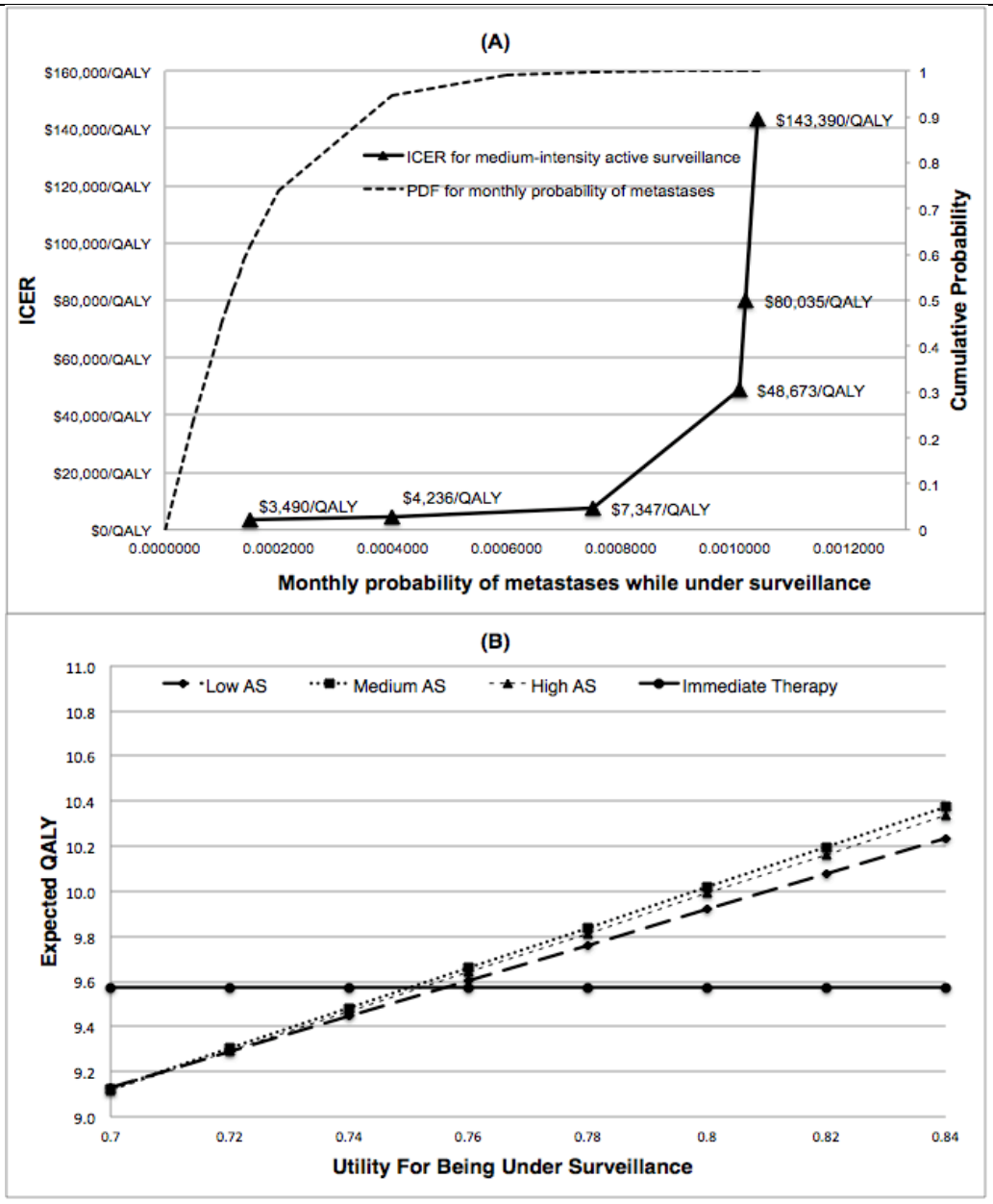
Table 1.6: Analysis with Modified Low-Intensity Protocol Included – Results for 65-yo Men with Low-Risk Disease

Protocol	Cost	QALY	ICER ($/QALY)	Dominance
Immediate Treatment	~~22,988~~	~~9.574~~	-	Dominated
Low-intensity AS	~~24,890~~	~~10.053~~	-	Dominated
Modified Low-intensity AS	21,399	10.194	-	Dominant
Medium-intensity AS	~~25,065~~	~~10.169~~	-	Dominated
High-intensity AS	~~36,638~~	~~10.137~~	-	Dominated

Note: Costs and QALYs discounted at 3% p.a.

Results when the fourth (modified low-intensity) AS protocol was included in the comparison were quite different from the base case. Notably, the removal of the confirmatory biopsy at 12 months after protocol initiation, and a change to a consistent semi-annual (rather than quarterly) DRE and PSA test specified in the modified low-intensity protocol, increases efficiency. With these changes the modified low-intensity protocol is the dominant strategy offering greater QALY (10.194) at a lower cost ($21,399) than any other protocol. (Table 1.6)

Figure 1.2(a) & (b): Sensitivity Analyses



(A) Sensitivity Analysis – Metastases while under AS. at varying values of probability of progression to metastatic disease while under active surveillance; Dashed line – Expected probability that frequency of metastases is less than modeled value

(B) Sensitivity Analysis – Utility for AS. Expected QALY for each strategy under varying assumptions about individuals' utility preferences for being under active surveillance

Discussion

Four-fifths of newly diagnosed prostate cancers are low volume Gleason 6 cancers, or so-called “low-risk” disease, which can often be effectively managed with active surveillance. There is evidence to suggest that these cancers present very little risk of metastasis and that delaying treatment does not increase this risk appreciably, yet fewer than 20% of men are undergo active surveillance. A study of 14,123 men with pathologic Gleason 6 disease identified only 22 cases with lymph node metastases.[82] Another study of 11,521 men treated with radical prostatectomy with confirmed Gleason 6 disease had a prostate cancer mortality of only 0.2%-1.2% at 15 years.[83] An additional study with a median follow up of 8 years, reported that the relative risk for non-prostate cancer death was 10-fold higher than that from prostate cancer. About one-third of patients enrolled on active surveillance will be reclassified to higher risk during their follow up. However, this reclassification appears to have little impact on overall survival, highlighting that active surveillance is effective at identifying progressive disease while still early enough to be successfully treated.

There is no consensus regarding the appropriate intensity of active surveillance. Both AUA and EAU guidelines recommend active surveillance in low-risk disease, but neither guideline specifies a protocol. The potential health benefits that would accrue from identifying the most appropriate surveillance protocol are considerable. The challenge is to select the least intense and costly surveillance protocol without compromising potential curability.

Clinicians seeking reassurance as to how to proceed when selecting a protocol may find our analysis useful. It illustrates that all three commonly reported AS protocols offer superior quality-adjusted outcomes and expected survival outcomes than immediate treatment.

Our model shows that medium-intensity AS offers a 217 quality-adjusted life-day improvement over the current US practice of immediate treatment of various modalities, at an incremental cost of $2,077 per man. The majority of this gain in quality-adjusted survival arises because the average patient initiating medium-intensity AS will delay treatment for 56 months, thereby deferring any adverse effects of treatment. Our analysis is sensitive to individual preferences. If preferences are such that utility while under active surveillance is less than 0.75, immediate treatment becomes the preferred strategy.

Our model suggests that improvements to the low-intensity AS protocol may be achieved by decreasing its intensity further, in turn making it the optimal strategy in terms of quality-adjusted survival and cost. This arises because the disutility from an increased rate of complications from more frequent biopsies outweighs the gains achieved through the small number of cancers that are prevented from metastasizing in the interval between biopsies. The inefficiency of the low-intensity AS (protocol) in our model is eliminated and reversed when the frequent monitoring in the first two years after diagnosis is eliminated. These protocol modifications may need to be applied on a patient-specific basis, since not all clinicians or their patients may be comfortable with

the extended wait until the first surveillance biopsy. The finding regarding this modified low-intensity AS protocol should be regarded as tentative, because it is not widely practiced, but our model suggest that it deserves further consideration by clinicians who favor a low-intensity approach,

The primary concerns for a clinician in recommending active surveillance are that cancer may progress or that metastases may occur, leading to worse outcomes, yet the data on metastases in untreated men is inconsistent. Currently available studies report mostly on watchful waiting to identify probabilities for these events; this can be misleading. The goal of watchful waiting is palliation of symptomatic disease; therefore, it is very likely that should a man live long enough, progression and metastases will occur.

For this reason, we modeled the probability of metastatic disease in monitored patients using a time-varying non-linear risk distribution to capture this characteristic[10]. Our analysis is consistent with the published literature in finding that metastatic disease is infrequent among low-risk patients. Further, our deterministic sensitivity analysis finds that the actual probability of metastases would have to be seven-fold higher than the expected value (the 99.97-th percentile) of our meta-analysis on the parameter for medium-intensity AS to no longer be cost-effective. We feel confident that our results

[10] In the case of probability of metastases while in an active surveillance protocol, we utilized several studies reporting frequency of metastases at different timepoints (in different untreated populations) to fit a Beta distribution. We then used this to draw values from at time, t=x, for time dependent parameters for a beta distribution. For example, at time point t=3 years, we drew from our Beta distribution to determine α and β for a beta distribution which was used to determine the outcome stochastically

are robust to changes in the frequency of metastases while under surveillance (Figure 2.2(a)).

The substantial gains in QALYs identified in our model lend further support to the case for medium-intensity AS with biennial biopsy frequency as the preferred treatment in this population given average preferences, or for a modified low-intensity protocol for those comfortable waiting a longer period between biopsies. This offers guidance to clinicians in the selection of appropriate monitoring strategies.

Future analyses should focus on further elucidating the advantages and disadvantages of extended intervals between surveillance biopsies, and to understanding patient preferences and utilities at the time a treatment choice is being made. Such preferences should be elicited on an ongoing basis in the case of active surveillance.

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Chapter 2

Surveillance Versus Initial Surgery in the Treatment of Papillary Thyroid Microcarcinoma: A Decision Model Comparing the ATA's 2015 and 2009 Guidelines

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Abstract

Importance

Diagnosis of thyroid cancer in the US has more than tripled since 1987, from 5.0 per 100,000 people, to 15.1 per 100,000 people in 2013. The majority of these patients present with small papillary tumors and have historically received Total Thyroidectomy as a treatment.

Objective

In 2015, the American Thyroid Association (ATA) released updated guidelines recommending Active Surveillance of certain small papillary tumors, and Lobectomy for larger unifocal tumors with no metastases. Clinicians may be interested in the outcomes from these treatments, and their relative clinical and economic performance compared to current standard of care, Total Thyroidectomy.

Design

We created a Markov microsimulation model to evaluate the performance of the ATA's 2015 guidelines compared to the ATA's 2009 guidelines. We modeled a cohort of 100,000 simulated patients with demographic and thyroid nodule characteristics representative of those presenting clinically in the US.

Main Outcome Measures

Life expectancy, QALYs, costs, and frequency of common surgical adverse events.

Results

In our base case analysis, we find that the ATA 2015 strategy dominates the ATA 2009 strategy. For all feasible combinations of model inputs in our probabilistic sensitivity analysis, the ATA 2015 strategy delivers greater discounted average QALYs [13.16 vs. 11.66] at a lower discounted average cost [$13,026 vs. $28,083].

Deaths due to Thyroid cancer under the ATA 2015 strategy are higher than the 2009 strategy [523 vs. 444], but this is entirely offset by a reduction in surgical deaths, leading to greater average life expectancy under the ATA 2015 strategy [83.40yrs vs. 83.36yrs]. Personal preference can have a significant influence on the optimal choice of strategy. Patients for whom Active Surveillance causes utility reductions of ≥ 0.126 achieve better results with the ATA 2009 strategy.

Conclusion

For eligible patients with papillary thyroid carcinoma, the ATA 2015 Guidelines represent a favorable treatment option. Clinicians should consider following these guidelines, especially for patients for whom Active Surveillance does not create a significant psychological concern.

Manuscript

Background

The incidence of thyroid cancer has been increasing in the United States. Rates have more than tripled since 1987, from 5.0 per 100,000 people, to 15.1 per 100,000 people in 2013[1]. In 2015, there were approximately 62,450 new cases in the United States[2]. Despite this increase in incidence, mortality has remained constant at 0.5 per 100,000 individuals over this same time period[3]. The reasons for this growing divergence between incidence and mortality are believed to be primarily due to increased use of cross-sectional imaging and technological advancements, as well as changing surgical and pathological practices – changes which allow for identification of what was an undiagnosed reservoir of smaller nodules and occult disease[1]. From 1975 to 2009, the proportion of incident papillary thyroid microcarcinomas (PTmC) – those tumors less than 10mm in largest diameter - increased from 25% to 39%[1]. This has led experts to question if we are over-treating patients with small, indolent tumors[1,4]. Research indicates that many PTmC are still treated aggressively with total thyroidectomy or radioactive iodine in the U.S[5]. Studies of active surveillance protocols with long term longitudinal follow-up in Japan have recently demonstrated that selected low-risk patients with PTmC can safely forgo surgery for small papillary thyroid cancers for periods of fifteen years or longer with no significant morbidity and no increase in disease-specific mortality[6–8]. In the small proportion of patients that had tumor progression or new lymph node metastases, excellent outcomes were observed with rescue surgery[6,7,9,10].

Additionally, it was recently reported that there was no difference in survival for patients undergoing thyroid lobectomy versus total thyroidectomy[11]. The use of lobectomy is intended to reduce the frequency of adverse surgical events like bilateral recurrent laryngeal nerve injury, and post-operative morbidities such as hypoparathyroidism and hypothyroidism. Lobectomy has long-term advantages over total thyroidectomy as it allows patients to retain some natural thyroid function, but for this same reason it incurs some short-term disadvantages, since it reduces the accuracy of thyroglobulin (Tg) as a tumor marker, precludes the use of radioactive iodine ablation, and may lead to a small increased risk of recurrence in these patients due to the remaining functional thyroid tissue.

Table 2.1: Strategy characteristics for selected ultrasound and FNAB findings based upon nodule size.

Nodule Findings			Strategy Recommendations	
Ultrasound Suspicion Pattern	Nodule Size	FNAB Characteristic	ATA 2009	ATA 2015
High	N/A	Not Benign	Total Thyroidectomy	Lobectomy*
		Benign	Benign Monitoring	
Intermediate	<10mm	Not Benign	Total Thyroidectomy	Active Surveillance
		Benign	Benign Monitoring	
	≥10mm	Not Benign	Total Thyroidectomy	Lobectomy*
		Benign	Benign Monitoring	
Low	<15mm	Not Benign	Total Thyroidectomy	Active Surveillance
		Benign	Benign Monitoring	
	≥15mm	Not Benign	Total Thyroidectomy	Lobectomy*
		Benign	Benign Monitoring	
Very Low	<20mm	Not Benign	Total Thyroidectomy	Active Surveillance
		Benign	Benign Monitoring	
	≥20mm	Not Benign	Total Thyroidectomy	Lobectomy*
		Benign	Benign Monitoring	
Benign	N/A	N/A	Benign Monitoring	

*Lobectomy is recommended only for nodules that are not multifocal, and with no lymph node metastases. [12,13]

ATA Guidelines

These findings and others have led to a shift to less aggressive treatment of low-risk papillary thyroid carcinomas (PTC). In 2015, the American Thyroid Association (ATA) published a revision to the 2009 Management Guidelines for Patients with Thyroid Nodules[12,13] (Table 2.1). Whereas the ATA's 2009 guidelines suggest total thyroidectomy for malignant nodules of any size and lobectomy only to be considered for small (<1cm) nodules with very specific characteristics (low-risk, unifocal, intrathyroidal, no prior irradiation and no nodal metastases), their 2015 update provided the option for active surveillance (AS) or thyroid lobectomy for a broader range of low-risk PTCs, including but not limited to PTmCs[12,13].

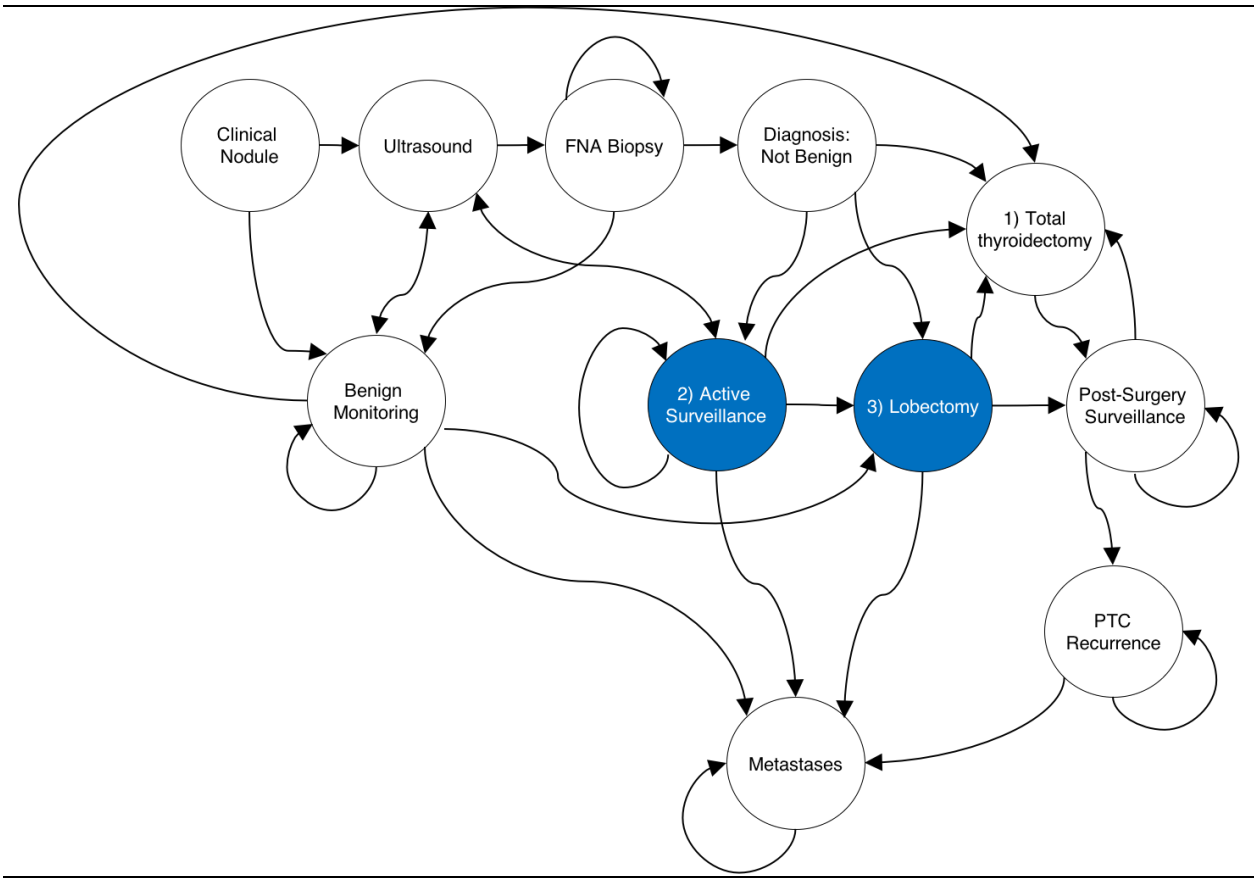
It is estimated that in 2006 approximately 23,000 of the 30,180 patients diagnosed with thyroid cancer in the U.S. underwent total thyroidectomy[14,15]. If surgery rates remain similar for 2016, we can expect initial treatment for patients diagnosed in 2016 to include nearly 48,000 total thyroidectomies at a total cost of approximately $660M to the US healthcare system[16]. Implementation of the ATA's 2015 guidelines should lead to a reduction in the number of total thyroidectomies, fewer surgical complications, and potentially, cost reductions. There will also be a subset of patients opting for AS that will have surgery delayed – in many cases indefinitely. In fact, several studies of patients with small PTCs have demonstrated that rates of disease progression, nodal metastases and distant metastases are exceedingly low and that many patients can avoid surgical intervention for substantial periods of time[6,9,17]. On the other hand, long-term outcomes including adverse effects on health-related quality of life and potential consequences of delayed or missed treatments are yet to be studied.

Nevertheless, it remains unclear whether the new ATA 2015 guidelines, if followed, represent a cost-effective strategy compared to the prior version. To date, no studies have evaluated both costs and effectiveness of the 2015 guidelines. We undertook a decision analysis comparing costs and effectiveness of the 2009 and 2015 guidelines to determine which strategy is more efficient in a representative US population.

Methods

We created a Markov state-transition patient-level microsimulation model in TreeAge Pro 2016, version 16.2.1.0-v20160817 to compare two strategies for managing patients with thyroid nodules. A schematic of the model structure is shown in Figure 2.1.

Figure 2.1: Markov Decision Model Schematic



For each state, we utilized a state-specific cycle duration, varying from 1 day for ultrasound to 365 days for post-surgery surveillance. (Table 2.2). We modeled the ATA's 2009 guidelines and compared them to the 2015 guidelines. All other statistical analyses were undertaken in R Statistical software version 3.1.

Table 2.2: Markov State Cycle Lengths / Durations used in Base Case

State	Cycle Duration
Active Surveillance	365 days
Benign Monitoring	365 days
Initial Diagnosis / Clinical Nodule	90 days
FNA Biopsy	1 day
Lobectomy Surgery	30 days
Metastases	365 days
Post-surgery Surveillance	182.5 days
Recurrence	365 days
Total Thyroidectomy Surgery	30 days
Ultrasound	1 day

We simulated a representative US cohort of 100,000 patients, distributed according to age, nodule size, nodule characteristics, and sex as reported in the literature[18]. Thyroid nodule characteristics such as microcalcifications, multifocality, solid or spongiform composition, hypoechogenicity, eccentric shape, and true underlying malignancy status were modeled on those found in populations reported in prior studies[19,20]. For each patient, a tumor growth type (growing, stable, shrinking) and rate is assigned probabilistically through a distribution derived from a regression model we created using a longitudinal cohort of Japanese patients undergoing active surveillance. Details of this regression analysis are provided in Appendix 2. While the Japanese patient data are the most relevant data we have available, we believe that these may

underestimate the true rates of progression due to some potential sample selection bias.

We used 2013 life tables from the United States Social Security Administration to model background mortality risk[21]. We discounted QALYs and costs at the standard 3% annual rate[22]. We utilized distributions to represent uncertainty in our parameter estimates and to allow for probabilistic sensitivity analysis (see Table 2.3 for details).

Table 2.3: Model Parameters

	Value	Distribution	Source
Utilities			
Airway Problem During Surgery	-0.500	None	Estimate
Bilateral RLN Injury	0.205	None	[58,59]
Diagnosis	-0.040	None	[59]
FNA Biopsy	-0.500	N/A	Estimate
Hematoma during surgery	-0.500	N/A	Estimate
Hypoparathyroidism	0.836	Uniform	[58,60,61]
Hypothyroidism	0.830	Beta	[61,62]
Distant metastatic disease	0.250	N/A	Estimate
Cancer Recurrence	0.540	N/A	[58]
Unilateral RLN injury	0.627	N/A	[58,61,62]
Probabilities			
Patient age at diagnosis	55.78	Normal (SD 11.68)	Estimate
Initial Tumor Size	21mm	Lognormal	[18]
Male Sex	14%	N/A	[18]
Annual discount rate	3%	N/A	N/A
TSH Range	0.5 – 5	Triangular	[63,64]
Recurrence in contralateral lobe (Lobectomy)	0.145		[41]
Death from distant metastases	0.077	Beta	[65]
Surgical death (Lobectomy)	0.0023	Beta	[46]
Surgical Death (Total Thyroidectomy)	0.0020	Beta	[45,46]
Distant Metastases at Initial Diagnosis	0.014	Beta	[11,27–33]
Lymph Node Metastases at Initial Diagnosis	0.268	Beta	[6,11,27–33,35,36,43]
Airway Problem (Lobectomy)	0.006	Beta	[46]
Hematoma (Lobectomy)	0.004	Beta	[46]
Hypocalcemia (Lobectomy)	0.023	Beta	[46]
Hypothyroidism (Lobectomy)	0.143	N/A	[66]
Hypoparathyroidism (Lobectomy)	0.022	Beta	[35,41,45,47,51,52]
Temporary Unilateral RLN Injury (Lobectomy)	0.015	Beta	[41,46,49–51]
Distant Metastases under Active Surveillance	0.007	Beta	Estimate / [9]
Distant Metastases under Benign Monitoring	0.005	Beta	Estimate
Ipsilateral LN Metastases	0.003	None	[9]
Distant Metastases post-surgery (Lobectomy)	0.005	Beta	Estimate

Distant Metastases post-surgery (Thyroidectomy)	0.005	Beta	Estimate
Distant Metastases during PTC recurrence	0.080	Beta	[13]
Contralateral LN Metastases (Lobectomy)	0.001	N/A	[9,41]
Multifocal Disease	0.424	N/A	[11]
Recurrence After Lobectomy	0.009	Beta	[27–31,33–38,40,41,43,55]
Recurrence after Thyroidectomy	0.008	Beta	[27–31,33–38,40,41,43,55]
Remission during recurrence	0.100	N/A	Estimate
Airway Problem (Thyroidectomy)	0.009	Beta	[46]
Hematoma (Thyroidectomy)	0.007	Beta	[41,45,46,54]
Hypocalcemia (Thyroidectomy)	0.141	N/A	[45,46,49,54]
Hypothyroidism (Thyroidectomy)	1.000	N/A	Estimate
Hypoparathyroidism (Thyroidectomy)	0.089	Beta	[35,41,51–53]
Unilateral RLN Injury (Thyroidectomy)	0.015	Beta	[41,45,46,49–54]
Bilateral RLN Injury (Thyroidectomy)	0.003	Beta	Estimate
Costs			
Ablation	$73.68	N/A	[67]
Airway problem	$5,790.24	N/A	[67]
CT Scan	$287.11	N/A	[67]
Endoscopy	$128.48	N/A	[67]
FNA Biopsy	$497.78	N/A	[67]
Hematoma	$5,790.24	N/A	[67]
Hypoparathyroidism (Annual)	$1,651.18	N/A	[67]
Hypothyroidism (Annual)	$158.03	N/A	[67]
cLT4Annual	$111.83	N/A	[67]
Metastatic Disease Treatment (Initial)	$60,196.00	N/A	[68]
Metastatic Disease Treatment (Ongoing)	$35,189.00	N/A	[68]
Primary Care Physician Visit	$96.96	N/A	[68]
Radioactive Iodine Treatment	$6,097.09	N/A	[64,67]
Bilateral Permanent RLN Injury	$27,874.28	N/A	[16]
Unilateral Permanent RLN Injury	$6,623.08	N/A	[16]
Unilateral Temporary RLN Injury	$2,224.24	N/A	[16]
Serum TSH Test	$23.10	N/A	[67]
cSpecialistVisit	$145.72	N/A	[67]
Lobectomy Surgery	$9,185.00	Lognormal	[69]
Surgical Mortality	$55,983.11	Gamma	[52]
Thyroidectomy	$11,352.00	Lognormal	[69]
Temporary Hypoparathyroidism	$867.77	N/A	[67]
Thyrogen	$2,103.80	N/A	[67]
Thyroid Scan	$332.65	N/A	[67]
Ultrasound	$124.86	N/A	[67]

Calibration is a well-established practice used to ensure that even in cases when robust data on some parameters are lacking, models are representative of outcomes observed in the real world. This is often achieved by aligning well-understood intermediate parameters generated by the model with real-world estimates of these

parameters. In our model, we manually calibrated parameters to reproduce point estimates of cancer-specific survival (CSS) at 5 years and at 15 years reported via the Surveillance Epidemiology and End Results (SEER) program and American Cancer Society (ACS) statistics[23,24]. Rates of metastases for untreated (but monitored as benign, or managed under AS) malignancies were adjusted to satisfy calibration targets, as these data on metastases rates are unknown or unknowable[25,26].

To simulate the biological variation between patients, and to determine the effect of uncertainty in our parameters, we undertook both probabilistic and deterministic sensitivity analysis. For our probabilistic sensitivity analysis, we ran 1,000 iterations of the model, each time with 100,000 simulated patients. For each iteration we used a unique parameter set sampled from our parameter distributions to simulate population and biological heterogeneity and parameter uncertainty. We averaged over all simulations to determine mean costs (US$) and effectiveness (life expectancy and quality adjusted life years, QALYs) for each strategy. We compared strategies using incremental cost-effectiveness ratios (ICER).

Deterministic sensitivity analysis entails deliberately varying one or more parameters over a range of possible values to determine the extent of the variation in the output caused by changes in the parameters. We undertook one-way deterministic sensitivity analysis on the rate of metastases while in an AS protocol, and separately, analysis of the reduction in patient utility while in an AS protocol, to measure the effect of changes in these two uncertain parameters.

Model Strategies

Common Elements

For both the ATA 2009 and ATA 2015 strategies, patients enter the model with a clinically recognized thyroid nodule which may be malignant or benign (underlying true state). An initial evaluation is undertaken utilizing serum thyroid stimulating hormone (TSH) and a thyroid scan for those patients with a suppressed TSH or “hyperthyroid”. Patients with a hyperfunctioning nodule are presumed to have a benign nodule and subsequently undergo monitoring for a benign nodule according to the standard of care. At this stage, patients with cancer can present with distant metastases at a rate which we determined via pooled analysis of several studies. Those patients move immediately to treatment for metastatic thyroid cancer[11,27–33].

Patients will undergo a neck ultrasound, at which time a pattern classification ranging from benign to very high suspicion based on the TIRADS classification and/or ATA guidelines is determined[13]. Patients with nodules classified as benign on ultrasound are monitored annually via ultrasound and physician evaluation for increases in nodule volume. Any nodule increasing in volume by 50% or more is treated with surgery, the aggressiveness of surgery (either lobectomy or total thyroidectomy) being determined by the specific strategy modeled.

In each case, patients undergoing surgery are subject to complications arising from surgeries. We included hematoma, hypocalcemia, hypoparathyroidism, hypothyroidism, recurrent laryngeal nerve (RLN) injury and operative mortality. Surgical complications, and their costs and probabilities, are shown in Table 2.3.

Patients are tracked after surgery, and any long-term surgical complications (hypocalcemia, hypoparathyroidism, hypothyroidism, recurrent laryngeal nerve injuries) are incorporated into their ongoing quality of life. Unlike those who undergo total thyroidectomy, patients who undergo lobectomy can develop tumor recurrence or *de novo* tumor in the contralateral thyroid lobe. All patients are subject to risk of recurrence in the operative bed, and of cervical lymph node and/or distant metastases based on rates in the literature (Table 2.3). Patients with recurrence of their tumor will undergo radioactive iodine treatment (or a second treatment in case of presentation with ≥ Stage III disease) initially based on RAI guidelines.

ATA 2009 Strategy

Within the ATA 2009 strategy, all patients undergoing ultrasound evaluation with nodules ≥ 10mm will additionally undergo fine needle aspiration biopsy (FNAB). The results of the ultrasound and FNAB lead to a determination that the nodule is either benign or malignant utilizing the Bethesda cytologic scale. If the nodule is determined to be malignant, the patient undergoes total thyroidectomy and radioactive iodine ablation, leading to the need for long-term treatment for hypothyroidism in addition to treatment for any other side effects of surgery.

ATA 2015 Strategy

In contrast to the ATA 2009 strategy, patients who follow the ATA 2015 protocol strategy undergo ultrasound, but criteria for FNAB changed. Based on a combination of ultrasound findings and nodule size, patients are either classified as “benign”, “active surveillance” or “malignant”. Any patient with a nodule classified as benign on ultrasound foregoes FNAB and is treated for a benign nodule. If not deemed benign,

patients undergo FNAB based upon various combinations of ultrasound findings and nodule size, and the Bethesda cytologic classification is determined. The interventions recommended for each type of patient under the ATA 2015 strategy are shown in Table 2.1. Smaller unifocal nodules with no lymph node metastases are recommended for AS. Patients with larger unifocal tumors and no lymph node metastases receive lobectomy -- others receive total thyroidectomy.

Model Inputs

Probabilities

All model probabilities except those modified through calibration were estimated from secondary sources (Table 2.3).

To determine PTC recurrence rates after each type of surgery we conducted a pooled analysis of seventeen studies reporting on 49,607 total thyroidectomy patients and 12,332 lobectomy patients[27-31,33–44] (Appendix 2).

Table 2.4: Pooled Analysis of Distant and Lymph Node Metastases at diagnosis

		Distant Metastases			Lymph Node Metastases		
		Total Patients	Distant Metastases	%	Total Patients	Lymph Node Mets	%
Mantinan	2012	91	1	1.10%	91	4	4.40%
Pelizzo	2006	359	1	0.28%	359	75	20.89%
Caliskan	2012		-		828	218	26.33%
Kim	2015	2372	11	0.46%	2372	932	39.29%
Ardito	2013	149	1	0.67%	149	15	10.07%
Cho	2012		-		205	45	21.95%
Cho	2012		-		322	49	15.22%
Pelizzo	2004		-				
Pedrazzini	2013	231	1	0.43%	231	73	31.60%
Siddiqui	2016		-		86	20	23.26%
Gülben	2008		-		81	10	12.35%
Appetacchia	2002		-				
Haigh	2004	5432	64	1.18%	5432	1396	25.70%
Bilimoria	2007	43917	968	2.20%			
Bilimoria	2007				44732	13307	29.75%
Ito	2003				626	121	19.33%
Adam	2014	61775	584	0.95%	61775	15134	24.50%
Pooled		**114326**	**1631**	**1.43%**	**117289**	**31399**	**26.771%**

For probabilities of complications arising from each type of surgery, we used data from fifteen different studies representing 23,628 lobectomy patients and 40,693 total thyroidectomy patients to undertake pooled analyses[35,41,45–54]. For each surgical complication, between 903 and 40,265 patients were analyzed. In each case, we generated a beta distribution utilizing the data within the pooled analysis, and included this distribution in our model to permit probabilistic sensitivity analysis.

Rates of initial distant and lymph node metastases were determined via pooled analysis (Table 2.4). Eight studies reported on the rates of distant metastases among 114,326 unique patients, and fourteen studies among 117,829 patients reported on rates of lymph node metastases[6,11,27–38,43]. Only four studies report on rates of metastases while under AS but still provide a sample of over 1,235 patients for durations of up to nearly 20 years [6–10]. Patients under AS tend to be healthier, and to have less advanced disease. Typically, those with multifocal disease or lymph node metastases are excluded from AS, implying that rates for these patients should be lower. Conversely, we presume that less aggressive therapy must leave patients at least slightly elevated risk of metastases versus similar patients who have surgery. Each of these factors leads to different effects on the estimated rate of metastases for patients under AS. We presume that AS patients are exposed to a higher metastasis risk than they would be had they had surgery, but that they start from a lower absolute level of risk of metastases. We conduct deterministic sensitivity analysis on this parameter due to the opposing nature of these two potential drivers of the outcome and our lack of a clear rationale to favor one over the other.

For other parameters, we created distributions with estimates of mean and variance determined from the literature. These distributions enabled us to simulate heterogeneity and parameter uncertainty. In cases where it was reported, we used sex-specific probabilities (e.g. initial tumor size and features). Details of the distributions are shown in Table 2.3.

Utilities

Utilities are numerical values, ranging from 0 (death), to 1 (perfect health) used to indicate preferences, or Quality of Life (QoL) in a given health state. Each future year is given a utility value, or QALY score which depends on the health state(s) of the patient during that year. Values accruing in future years are discounted to reflect their diminished value compared to immediate QALY gains. QALYs for each individual patient in the model are computed by summing over years. Finally, QALYs for individual patients are summed to determine total discounted expected QALYs gained under each strategy. Utilities were estimated for all complications and all health states. Data for utility values were taken from secondary literature where available. In the case of patient utility for active surveillance, we conducted sensitivity analysis on this parameter due to its potential significance in the model.

Patients who undergo surgery are exposed to surgical complication risks, and the associated disutility that accompanies the complication. For each short-term surgical complication we estimated the disutility, and applied the disutility for the appropriate duration and summed this into the patient's total lifetime QALYs. We modeled the duration of complications due to each of the treatments as either short-term or long-term adverse effects. Short-term complications included: airway problems, hematoma,

hypocalcemia, hypoparathyroidism, hypothyroidism, and both unilateral and bilateral recurrent laryngeal nerve (RLN) injury. Long-term complications included hypocalcemia, hypoparathyroidism, hypothyroidism, and both unilateral and bilateral recurrent laryngeal nerve (RLN) injury. We presumed short-term surgical adverse effects persist during the surgical recovery period of 30 days, and long-term adverse effects persist for the patient's lifetime.

Costs

Costs were estimated from the published literature, the Centers for Medicare and Medicaid Services (CMS) Fee Schedule, the fee schedule at a major academic hospital, and CMS' National Inpatient Sample (NIS) database. In each case we determined costs using a set of CPT, ICD-9-CM or ICD-10 codes for subcomponents of the procedure or treatment. Author CL provided detail on contents of bundled procedures, allowing for individual components of cost to be obtained from Redbook (drug costs), CMS Fee schedule (physician services), and NIS (hospital procedures). Costs of FNA Biopsy, Lobectomy and Total Thyroidectomy were obtained using 2014 data from AHRQ's NIS database for ICD-9-CM codes 06.2 and 06.4.

It is rare for patients to develop metastases. When this occurs, treatment costs often escalate significantly. Additionally, costs related to surgical mortality can vary substantially. For these parameters, we utilized lognormal (for surgery) and gamma (for surgical deaths) distributions to model the variation and the potential for very high cost patients.

Results

Base Case

Our base case analysis modeled a cohort of 100,000 patients with mean age 56 years, 86% female sex and having thyroid nodules with mean size 21mm to reflect the range of individuals most representative of the patient population seen in clinical practice. For this cohort, ATA 2015 was the cost-effective strategy and dominated ATA 2009, generating greater average QALYs [13.16 vs. 11.66] at a lower average cost per patient [$13,027 vs. $28,083]. Results are shown in Table 2.5.

Table 2.5. Results of Base Case Analysis

Protocol	Cost	QALY	ICER	Dominance
ATA 2009	28,083	11.66	-	-
ATA 2015	13,027	13.16	-	Dominant

The lifetime risks of distant metastatic cancer under the ATA 2015 and ATA 2009 strategies (including those with distant metastases at initial diagnosis) were 3.13% and 2.88%, the risks of death from thyroid cancer among all patients were 0.84% and 0.71%, and the lifetime cancer-specific death probabilities among patients with malignant nodules were 6.92% and 5.88%.

Additionally, there is a significant decrease in the number of surgical deaths, acute adverse events, and long-term complications among the ATA 2015 strategy patients. In each case, these events are approximately 1/3 or less of those seen in the ATA 2009 strategy due to fewer patients at risk and lower complication rates. Average patient life expectancy slightly favored the ATA 2015 strategy (83.40 years vs. 83.36

years). In the case of the highly-morbid permanent bilateral recurrent laryngeal nerve injury, rates under the ATA 2015 strategy are only approximately 4% of those in the ATA 2009 strategy (0.05% vs. 1.2%). Full results are shown in Table 2.6.

Table 2.6. Results of Base Case Analysis – Predicted Numbers of Events Under Each Strategy. Based on 2016 US Thyroid Cancer Incidence (62,450 patients)

	Strategy	
Outcome	ATA 2009	ATA 2015
Diagnostic:		
FNA Biopsies (Lifetime)	80,132	18,555
Initial Benign Diagnosis	34,953	18,248
Treatment:		
Patients Under Active Surveillance	0	43,483
Total Thyroidectomies (Lifetime)	51,298	2,049
Lobectomies (Lifetime)	0	14,655
Surgeries (Lifetime)	51,298	16,704
Treatment-Related Adverse Events:		
Surgical Airway Problems	460	102
Surgical Hematomas	367	78
Temporary RLN Injuries	761	248
Permanent RLN Injuries (Unilateral)	332	111
Permanent RLN Injuries (Bilateral)	136	5
Surgical Deaths	102	38
Outcomes:		
Life Expectancy	83.36 years	83.40 years
Locoregional & Lymph Node Metastases	9,790	11,364
Distant Metastases	1,800	1,952
Cancer Deaths	444	523
Combined Cancer and Surgical Deaths	546	561

Sensitivity Analysis

In probabilistic sensitivity analysis, which involved varying multiple parameters simultaneously within the model to determine the effect of different combinations of uncertain inputs, the ATA 2015 strategy was preferred with certainty for all values of willingness to pay (WTP) of $0 or greater due to its dominance in all iterations.

We hypothesized that the comparative effectiveness of the two strategies would depend on patients' utility while under AS, since patients with strong preferences for immediate treatment are unlikely to be good candidates for AS. For this reason, we undertook deterministic sensitivity analysis on the parameter used to track patients' utilities while under AS. We find that if an individual patient's disutility for AS is more than 0.126, the patient should be treated immediately. (Figure 2.2).

Finally, we undertook deterministic sensitivity analysis on rates of metastases while under AS. We find that model results are insensitive to changes in this parameter. (Figures 2.3 & 2.4).

Figure 2.2: Sensitivity Analysis. Changes in discounted lifetime utility (QALYs) for each strategy with varying rates of patient-specific utility for being under active surveillance

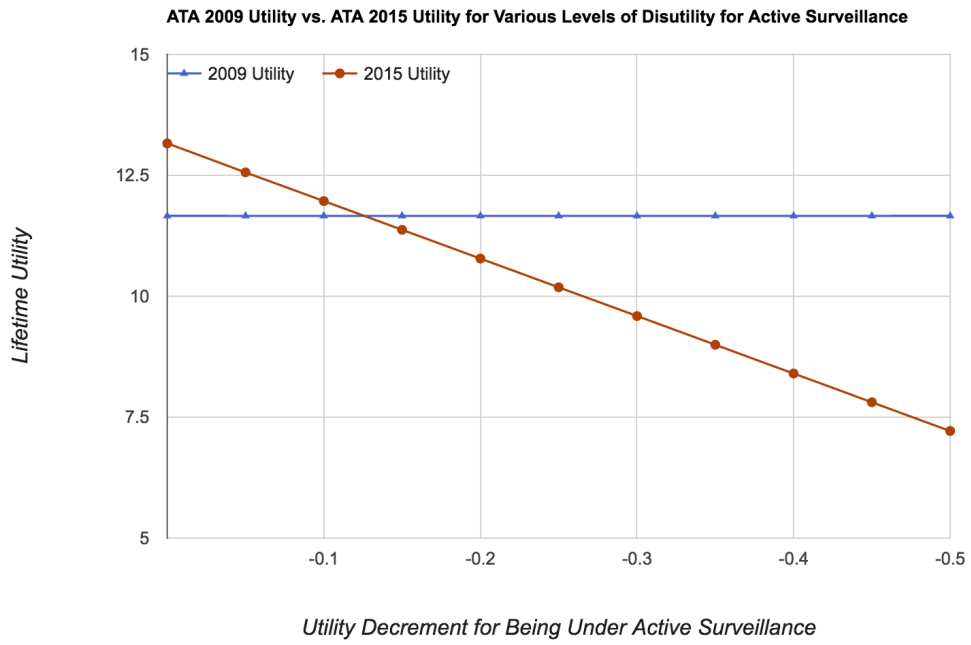


Figure 2.3: Sensitivity Analysis. Changes in discounted lifetime costs (USD$) of each strategy with varying rates of distant metastases while under active surveillance

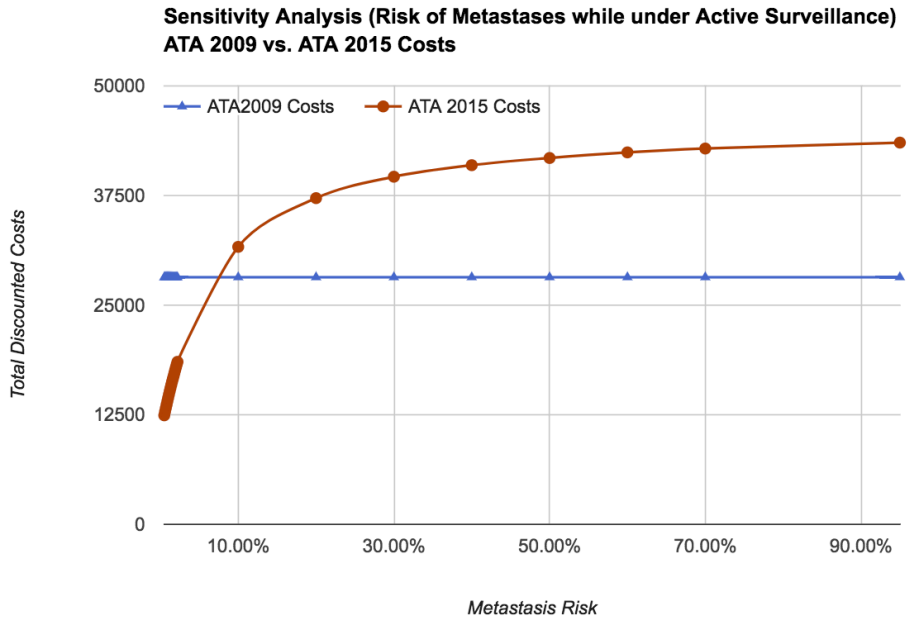
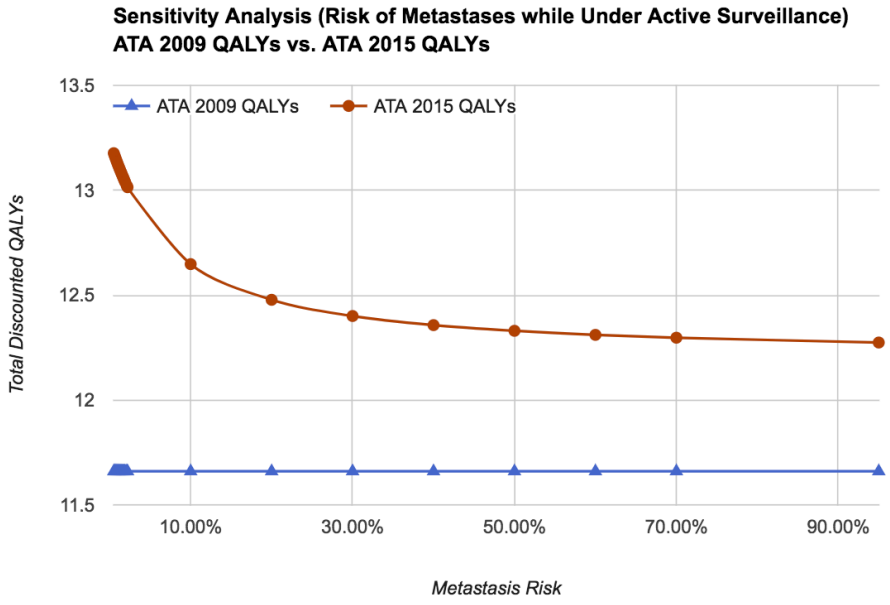


Figure 2.4: Sensitivity Analysis. Changes in Discounted Lifetime Utility (QALYs) for each strategy with varying rates of distant metastases while under active surveillance



Discussion

Our analysis showed that the ATA 2015 guidelines present a highly cost-effective alternative to the ATA's 2009 Guidelines. Use of the ATA 2015 recommended strategy would lead to far fewer surgeries and surgical complications, and greater quality of life. It would only have a small detrimental effect on overall rates of cancer-specific survival, an effect on average patient life-expectancy that is entirely offset by a reduction in surgical mortality.

In their attempt to address questions pertaining to these smaller tumors, changes to the ATA guidelines have promoted less intensive therapies for a subset of tumors satisfying size and ultrasound criteria. We estimate that approximately 43,500 of the 62,450 newly diagnosed patients in the US each year are suitable candidates for treatment via AS. We also find that under the ATA 2015 guidelines nearly 35,000 fewer patients would undergo surgery each year, and of these surgeries, nearly 88% of them would be lobectomies, a lower risk alternative to total thyroidectomy. We estimate that if the revised guidelines were followed, there is the potential for a large proportion of patients to be candidates for AS and for less aggressive surgery. The updated guidelines represent a potentially significant change in practice patterns. Thus, despite their expected benefit, clinicians will need reassurance that this move toward less intensive treatments will still offer patients excellent outcomes.

Within the updated guidelines modeled herein, two major changes may be of particular interest to clinicians: active surveillance as an option to delay treatment, and lobectomy as a less intensive, but still highly efficacious immediate treatment. Studies of

lobectomy for thyroid cancer report on many patients over a significant duration. These studies indicate that when applied to appropriate patients, generally those without lymph node metastases and having unifocal tumors, lobectomy offers nearly as favorable recurrence and survival outcomes as total thyroidectomy, but results in much lower morbidity[11,19,55]. Our model results suggest that even though approximately 14% of patients initially treated via lobectomy will require completion thyroidectomy at some juncture, the initial use of lobectomy among eligible patients leads to quality of life gains and reduced cost. Likewise, we acknowledge in practice that there are other indications for performing an initial thyroidectomy such as bilateral nodules and patient preference.

In contrast to lobectomy, there are relatively few studies reporting on the consequences of delaying intervention by using AS for PTC. Active Surveillance as a strategy has been in use for low-risk prostate cancer for many years now[56]. Similar challenges exist in determining appropriate candidates for PTmC active surveillance as exist in prostate cancer. While not all small PTmCs will be aggressive tumors, all large PTCs were small at one time, and criteria to predict which small tumors will become large tumors are not known.

Although AS of PTmC has been utilized in limited settings overseas, it is a relatively new phenomenon in the US and data are lacking on the risks associated with delaying treatment for patients with small well-differentiated papillary thyroid malignancies. Fortunately, the limited data available to date indicate highly promising results, with high cancer-specific survival rates observed even over extended durations. It appears that the criteria for AS can be made sufficiently strict that, as with prostate

cancer, treatment delays do not typically lead to bad outcomes, yet still allow application to a large proportion of patients. Results from PTC AS in Japan indicate distant metastasis rates of 0% for a cohort of 1,235 patients followed up to 227 months[9,10].

Our sensitivity analysis on rates of metastases while following an AS protocol indicates that even at simulated rates of metastases while under surveillance significantly higher than has been reported, the ATA 2015 guidelines are still strongly preferred. We believe that this is attributable to two facts: (1) in our model, only approximately 13% of patients under surveillance actually have a malignancy and are at risk of metastases, and (2) even for metastatic disease, the annual rates of mortality are still low at less than 8%, as reported by prior authors[42,57].

Almost inevitably, some patients eligible for AS and their physicians may still be uncomfortable delaying treatment despite our findings, and patient preference may have a significant influence on treatment choice. However, our sensitivity analysis on patient preference for AS indicates that our results are robust to reductions in patient utility of up to 0.126. Although patients with this strong a preference against AS may opt for immediate treatment, this has only a minor influence on the choice of strategy due to the presence of lobectomy as a treatment option in the ATA 2015 strategy. Patients who qualify for AS but have a strong preference for immediate treatment are almost certainly candidates for lobectomy. Due to lobectomy's lower rate of complications compared to total thyroidectomy, and comparable long-term outcomes in qualifying patients, the efficiency of the ATA 2015 strategy is maintained.

The results of our model indicate that the ATA 2015 Guidelines are a highly cost-effective strategy for management of patients with small, well-differentiated papillary thyroid cancers and should be preferred over the ATA's 2009 Guidelines. The use of AS reduces the frequency of serious adverse events arising from surgery. Preferential use of lobectomy in a subset of patients allows these patients to retain thyroid function and thereby avoid lifelong treatment for hypothyroidism. Further research into rates of metastases while under AS, and more specific clinical characteristics of suitable patients for AS, would be beneficial to further demonstrate the safety and applicability of this approach. Additional studies on the health-related quality of life for patients undergoing AS will be valuable.

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Chapter 3

Physician Adherence to JNC7 Hypertension Treatment Guidelines: An EMR Database Analysis

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Abstract

Purpose

Hypertension affects approximately 30% of US adults and is correlated with significant cardiovascular events. Despite clear and well-established guidelines for treatment, nearly half of the 75 million hypertensive individuals in the US remain insufficiently treated. We sought to determine the effect of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) guidelines on rates of antihypertensive medication prescribing among primary care physicians, and how rates of medication prescription for eligible patients varied by age, sex, race or comorbidity status.

Methods

We employed data from an electronic medical records database to undertake a logistic regression analysis. We analyzed 11.8 million blood pressure readings for adult patients (≥18 years) naïve to any antihypertensive medication and seen in outpatient clinics between January 2010 – December 2013. We investigated the effect of the JNC7 guideline by examining treatment in patients with blood pressure readings just above or below the treatment threshold (systolic pressure 135-144 mmHg for non-diabetics).

Results

Treatment eligibility based upon systolic blood pressure significantly drives the initiation of antihypertensive medication (OR = 2.97±0.02). Nevertheless, only between 17% and 36% of patients who satisfy the guideline for treatment are treated. For patients with blood pressure readings at or near the JNC7 guideline threshold, those

patients with qualifying systolic blood pressure readings (≥140mmHg, or ≥130mmHg for diabetics), have significantly higher odds of treatment than their non-qualifying counterparts (OR = 7.75±0.63)

Compared to non-treatment-eligible white patients aged 18-30 years old with no cardiovascular comorbidities, similar black and Hispanic patients have a higher likelihood of treatment (OR = 1.95±0.00 and 1.41±0.00, respectively), as do white patients aged 60-70 years old with no cardiovascular comorbidities (OR = 10.83±0.01) and white patients 18-30 years old with cardiovascular comorbidities (OR = 1.43±0.00).

Conclusion

Although JNC7 guidelines affect rates of pharmacologic antihypertensive treatment initiation, a substantial proportion of eligible patients do not receive guideline concordant antihypertensive therapy. Moreover, this proportion varies significantly by age, race and comorbidity status.

Manuscript

Introduction

Background

Hypertension is one of the most prevalent medical conditions in the United States, affecting approximately 30% of US adults and is correlated with significant cardiovascular events with high morbidity, mortality and costs[1,2]. Prospective and retrospective studies have shown that successful treatment of hypertension, and particularly, systolic blood pressure (SBP) control, leads to reductions in stroke, myocardial infarction, heart failure[3]. Appropriate diagnosis via blood pressure measurement, and effective treatment through the use of antihypertensive therapy, is associated with 35-40%, 20-25% and >50% reductions in incidence for these respective events[3]

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)[3], defines hypertension in those without diabetes or chronic kidney disease (CKD) as systolic blood pressure 140mmHg or greater (130mmHg for diabetic patients), or diastolic blood pressure 90mmHg or greater (80mmHg for diabetic patients). Blood pressure, a metric sufficient to implement the JNC7 guidelines, is easily measurable by healthcare providers using the sphygmomanometer available in almost every physician office. Despite this, studies indicate that even in high quality academic centers in excess of 30% of patients who meet hypertension diagnostic criteria are not appropriately diagnosed[4].

A large proportion of patients with hypertension therefore remain inadequately treated. In 2012, nearly 30% of US adults were hypertensive. Yet an estimated 54% of hypertensive patients did not have their blood pressure controlled either due to lack of treatment initiation, lack of adherence to treatment or insufficient treatment, despite clear guidelines and effective therapies[2]. Prior authors have evaluated treatment effectiveness and management of hypertensive patients[5–7]. This is the first study to evaluate rates of JNC7 concordant treatment initiation based upon blood pressure readings in a nationally representative population

JNC7 Guidelines

The JNC7 guidelines were released in 2004, approximately 7 years after their predecessor, the JNC6 guidelines. A key difference from the JNC6 guidelines was an effort to make the guidelines easy to apply. To this end, the committee specifically called for the guidelines to be more concise and for the criteria for diagnosis to be simplified[3] The JNC7 guidelines specify that non-diabetic patients with SBP ≥ 140mmHg or DBP ≥ 90mmHg be treated for Hypertension with pharmacologic therapy. For diabetic patients or those with chronic kidney disease, the SBP threshold for treatment with pharmacologic therapy is 130mmHg and DBP is 80mmHg.

We undertook an analysis to compare physicians' antihypertensive medication prescribing behavior with the recommended practice from the JNC7 guidelines. We also examined how guideline-concordant treatment initiation varied by patient characteristics such as patient gender, age, or race.

Methods

Data Source

Data were gathered from the GE Centricity Electronic Medical Records (GE-EMR) system's Medical Quality Improvement Consortium (MQIC) dataset. The MQIC is a consortium of over 700 ambulatory practices representing 33,000 healthcare providers caring for approximately 35 million patients throughout the United States. Data from these providers are collected as part of standard clinical practice. They are used to create the federally mandated "Meaningful Use" reports, population health management initiatives and quality reporting.

The GE-EMR has been in use for over 25 years and is certified by the Certification Commission for Healthcare Information Technology. It has been utilized in prior analyses, and validated against NCHS-NAMCS to show concordance in results for many conditions including hypertension and diabetes (24.4% and 10.2% for GE-EMR, 20.2% – 25.4% and 8.5% – 11.1% for NAMCS respectively)[8,9].

Records in the GE-EMR contain patient demographic information and patient clinical characteristics such as prior and current diagnoses and medication lists. During and post-visit, physicians record the details of the patient office visit encounter. This encounter record contains information pertaining to patient symptoms, diagnoses made, procedures performed and prescriptions written during the visit, as well as free text physician notes. For this analysis we relied solely on the structured information contained in the dataset. This structured data contains details of patient date of birth, gender, race, ethnicity, marital status, employment status, and pre-existing health conditions, as well as numeric blood pressure readings that were captured by the

clinician at the time of the visit. Importantly, the record also contains information regarding the patient's current medications allowing physicians to determine during the visit if a patient has reported any current pharmacologic treatment for hypertension.

Patient Population

Inclusion Criteria

All blood pressure readings recorded for adult patients (age ≥18) during an office visit with an Internal Medicine or Family Practice physician, or a Cardiologist within the period January 1, 2010 until December 17, 2013 were included in the initial extraction. This cutoff date was chosen to coincide with the publication of the updated JNC8 guidelines, which supplanted the JNC7 guidelines and defined a higher systolic blood pressure treatment threshold for older patients.

Exclusion Criteria

Data were excluded from analysis if patients were less than 18 years old at the time of the blood pressure reading, if patients' records indicated that they were taking any existing antihypertensive medications, if their blood pressure readings were likely incorrect (SBP < 100 or >200, DBP < 55 or > 120, SBP not at least 10mmHg greater than DBP), or if the reading was taken during a visit to a practice with a specialty other than those defined in the inclusion criteria.

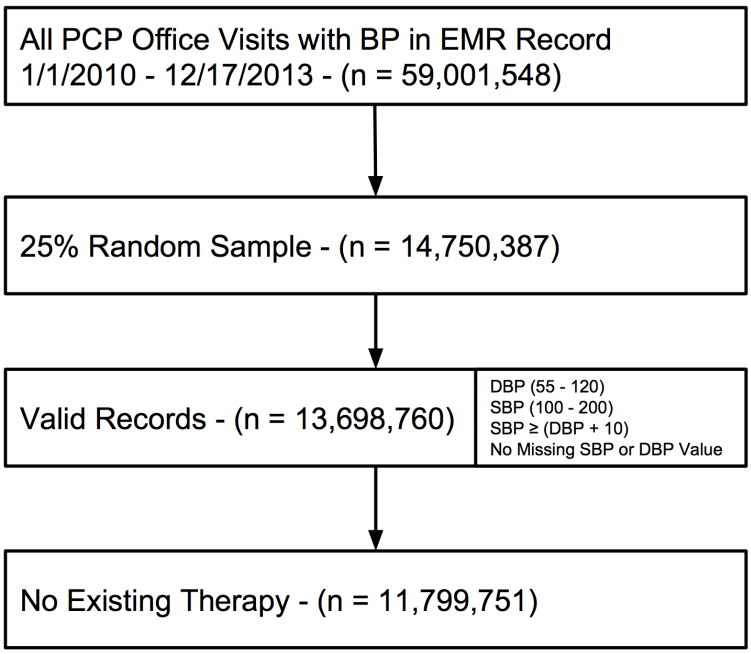
Data Elements

For each blood pressure reading in the dataset, the patient's gender, age, marital status, employment status, race and ethnicity were recorded. Additionally, we determined whether the patient was evaluated by a physician, or by a non-physician healthcare provider, and the medical specialty of the provider. For each patient's blood

pressure record, we determined whether any antihypertensive drug was prescribed for the patient during the office visit at which the blood pressure reading was taken. Medications considered suitable for hypertension treatment included those from the classes “Diuretics”, “Beta Blockers”, “Angiotensin Receptor Blockers”, “Angiotensin Converting Enzyme inhibitors” or “Calcium Channel Blockers”. Any medication from any of these classes prescribed at the time of the visit was sufficient to determine that guideline-concordant medication was prescribed.

Utilizing patient medical histories within the dataset, any patient with a history of ischemic heart disease (IHD), congestive heart failure (CHF), diabetes, myocardial infarction (MI), stroke (CVA) or peripheral vascular disease (PVD) was identified and flagged for subgroup analysis.

Figure 3.1: Dataset Inclusion Exclusion Criteria



Our initial dataset contained 59,001,548 patient blood pressure records within the eligible date range from eligible providers. After the application of all inclusion and exclusion criteria, the retained sample for analysis contained 11,799,751 patient blood pressure records. Dataset characteristics are shown in Figure 3.1 and Table 3.1.

Table 3.1: Dataset Characteristics (n= 11,799,751)

Blood Pressure – Mean (SD)	
Systolic	127.1 (15.2)
Diastolic	76.5 (9.6)
Patient Gender	
Female	0.60
Patient Age	
18 – 29	0.15
30 – 39	0.13
40 – 49	0.16
50 – 59	0.19
60 – 69	0.17
70 – 79	0.12
80 and older	0.07
Patient Race	
White	0.69
Black	0.08
Asian	0.02
Native American / Alaskan	0.00
Hawaiian / Pac. Islander	0.00
Unknown	0.17
Not-Entered	0.04
Patient Ethnicity	
Non-Hispanic	0.76
Hispanic	0.08
Unknown	0.17
Not Entered	0.00
Patient Employment Status	
Employed	0.15
Unemployed	0.06
Retired	0.11
Unknown	0.60
Not Entered	0.08
Patient Marital Status	
Married	0.48

Single	0.23
Widowed / Widower	0.07
Divorced	0.06
Separated	0.01
Partnered	0.00
Unknown	0.16
Not Entered	0.00
Comorbidities	
Diabetes	0.21
History of Myocardial infarction	0.02
History of Stroke	0.06
History of Ischemic Heart Disease	0.12
History of Peripheral Vascular Disease	0.04
History of Congestive Heart Failure	0.04
Treating Provider Type	
Physician	0.96
Non-Physician	0.04

Analysis of Effect of Guidelines

We conducted logistic regression analyses on the entire sample population, and then undertook separate subgroup analyses by age, gender, and comorbidity status.

Overall Analysis

If physician prescribing behavior was influenced by the sharp blood pressure threshold promulgated by the JNC7 guidelines, there would be a discontinuity in the rates of antihypertensive medication prescription at the DBP 90mmHg or the SBP 140mmHg thresholds. We searched for this discontinuity.

Our primary outcome of interest was physicians' antihypertensive drug prescribing behavior for their patients (prescription of any antihypertensive drug = 1). Independent predictor variables included in the model were systolic (or in a separate model, diastolic) blood pressure reading, patient 10-year age category (18 – 30, 30-40, 40-50, 50-60, 60-70, 70-80, 80+), gender (Male, Female), race (White, Black, Asian, Native American, Hawaiian/Pacific Islander), ethnicity (Non-Hispanic, Hispanic),

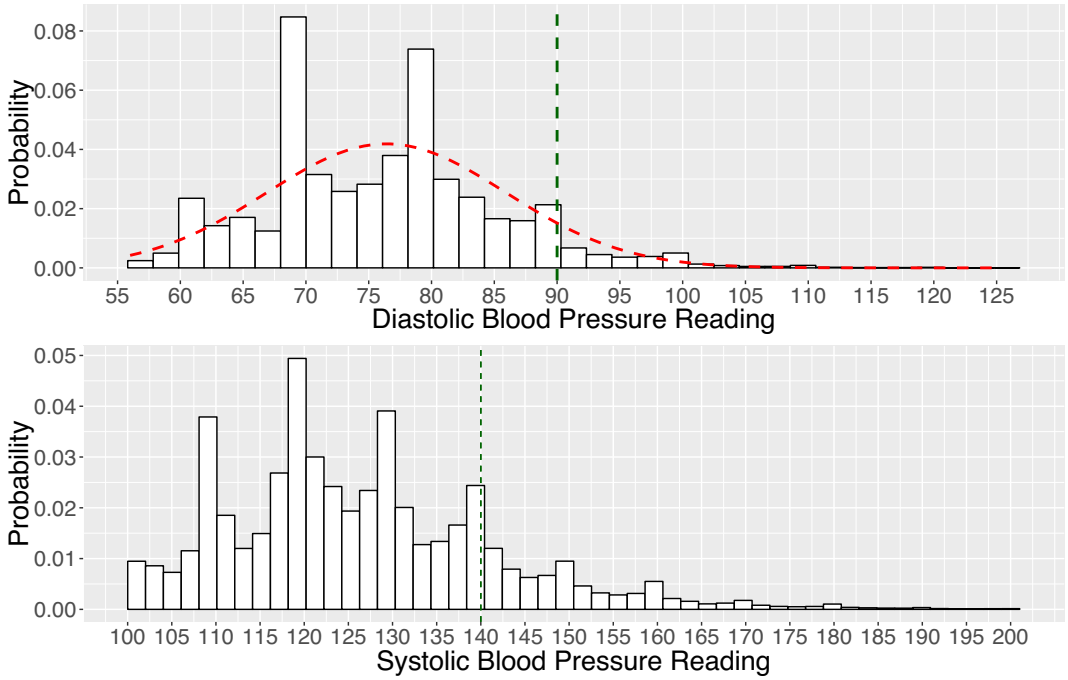
employment status (Unemployed, Employed, Retired), marital status (Married, Single, Widowed, Divorced, Separated, Partnered), existence of comorbidities (Yes/No), and whether the healthcare provider was a physician (Yes/No).

To test whether JNC7 guidelines affected prescribing behavior, in all model specifications we included a covariate indicating whether the patient satisfied the JNC7 guidelines of either 140mmHg systolic (130mmHg for diabetic patients) or 90mmHg diastolic for treatment (Treatment Eligible = 1). We also included an interaction term between systolic blood pressure and JNC7 guideline treatment eligibility to determine if physicians' response to systolic blood pressure was greater than their response to diastolic blood pressure.

Threshold Analysis

To determine the effect of the 140mmHg systolic cutoff on physicians' propensity to initiate antihypertensive therapy, additional logistic regression analyses were undertaken utilizing only those patient blood pressure records where systolic blood pressure readings fell in the range between 135mmHg and 144mmHg. Presuming the guidelines are effective, there should be a step change in prescribing probability for patients below 140mmHg compared to their near equivalent counterparts with SBP of 140mmHg (and above).

Figure 3.2: Distribution of systolic and diastolic blood pressure readings



Subgroup Analyses

Using the same model specifications, we undertook subgroup analyses by ten-year age group, gender and comorbidity status. All analyses were undertaken using R statistical software, version 3.3.

The study was approved by the Institutional Review Board of the Harvard Faculty of Arts and Sciences.

Results

Blood pressure distribution

The distribution of blood pressure readings highlighted a strong zero terminal-digit preference for both systolic and diastolic values (Figure 3.2). Readings with zero

end-digits were recorded 30% and 34% of the time for diastolic and systolic values respectively. Providers also had a preference for reporting even-numbered readings; even numbered readings were recorded in the dataset 86% of the time for both diastolic and systolic values. Controlling for other covariates, patients whose systolic blood pressure reading is even numbered have slightly greater odds of treatment (OR = 1.04±0.01). For diastolic blood pressure, the even-number effect was also small, but in the opposite direction (OR = 0.99±0.00).

Table 3.2: Overall Population Regression Analysis Results

	Systolic		**Diastolic**	
Sample Size	11,799,751		11,799,751	
	Estimate	SE	Estimate	SE
(Intercept)	0.001	0.019	0.003	0.016
Systolic BP (mmHg)	1.025	0.000	N/A	N/A
Diastolic BP (mmHg)	N/A	N/A	1.018	0.000
Treatment Eligible	2.972	0.023	0.833	0.016
Even Systolic BP Reading	1.039	0.003	N/A	N/A
Even Diastolic BP Reading	N/A	N/A	0.989	0.003
Physician	1.108	0.005	1.113	0.005
Gender				
Male	1.000		1.000	
Female	0.892	0.002	0.905	0.002
Race				
White	1.000		1.000	
Black	1.952	0.003	1.938	0.003
Asian	1.540	0.007	1.503	0.007
Native American	0.894	0.016	0.889	0.016
Hawaiian / Pacific Islander	1.225	0.021	1.204	0.021
Unknown	1.211	0.003	1.215	0.003
Not Entered	1.047	0.005	1.050	0.005
Ethnicity				
Non-Hispanic	1.000		1.000	
Hispanic	1.411	0.004	1.422	0.004
Unknown	0.840	0.003	0.841	0.003
Not Entered	1.320	0.018	1.305	0.018
Marital Status				
Married	1.000		1.000	
Single	1.096	0.003	1.092	0.003
Widowed/Widower	1.103	0.004	1.118	0.004
Divorced	0.987	0.004	0.984	0.004
Separated	1.105	0.011	1.100	0.011
Partnered	0.818	0.072	0.803	0.072
Unknown	1.074	0.003	1.072	0.003
Not-Entered	1.599	0.173	1.538	0.174

Employment Status				
Unemployed	1.000		1.000	
Employed	0.957	0.005	0.960	0.005
Retired	0.828	0.005	0.841	0.005
Unknown	0.949	0.004	0.949	0.004
Not-Entered	0.937	0.005	0.946	0.005
Age Category				
Age 18-30	1.000		1.000	
Age 30-40	3.503	0.008	3.403	0.008
Age 40-50	6.788	0.007	6.727	0.007
Age 50-60	9.557	0.007	10.049	0.007
Age 60-70	10.830	0.007	12.379	0.007
Age 70-80	9.644	0.008	11.874	0.008
Age 80+	7.875	0.008	10.201	0.008
Comorbidities				
False	1.000		1.000	
True	1.430	0.002	1.435	0.002
Interaction	1.000		1.000	
Systolic BP (mmHg) * Treatment Eligible	0.992	0.000	1.007	0.000

In unadjusted regression models for the overall population there was a significant difference in physicians' response to increases in diastolic blood pressure for readings above the 90mmHg threshold for both diabetic and non-diabetic patients, indicating guideline effectiveness (Figures 3.3(a), 3.3(b), 3.3(c) & 3.3(d)). The effect is noticeable, but much less pronounced, for systolic blood pressure readings at the respective 130mmHg and 140mmHg thresholds. In all models, there were increasing odds of antihypertensive drug prescription with increasing systolic blood pressure and greater odds of prescribing for patients who satisfy the guideline criteria. For each 1mmHg increase in SBP the odds of treatment increase by 2.5%.

Figure 3.3(a)–(d): Threshold Analysis Results showing Systolic and Diastolic cutoffs for treatment and treatment probability above and below treatment thresholds

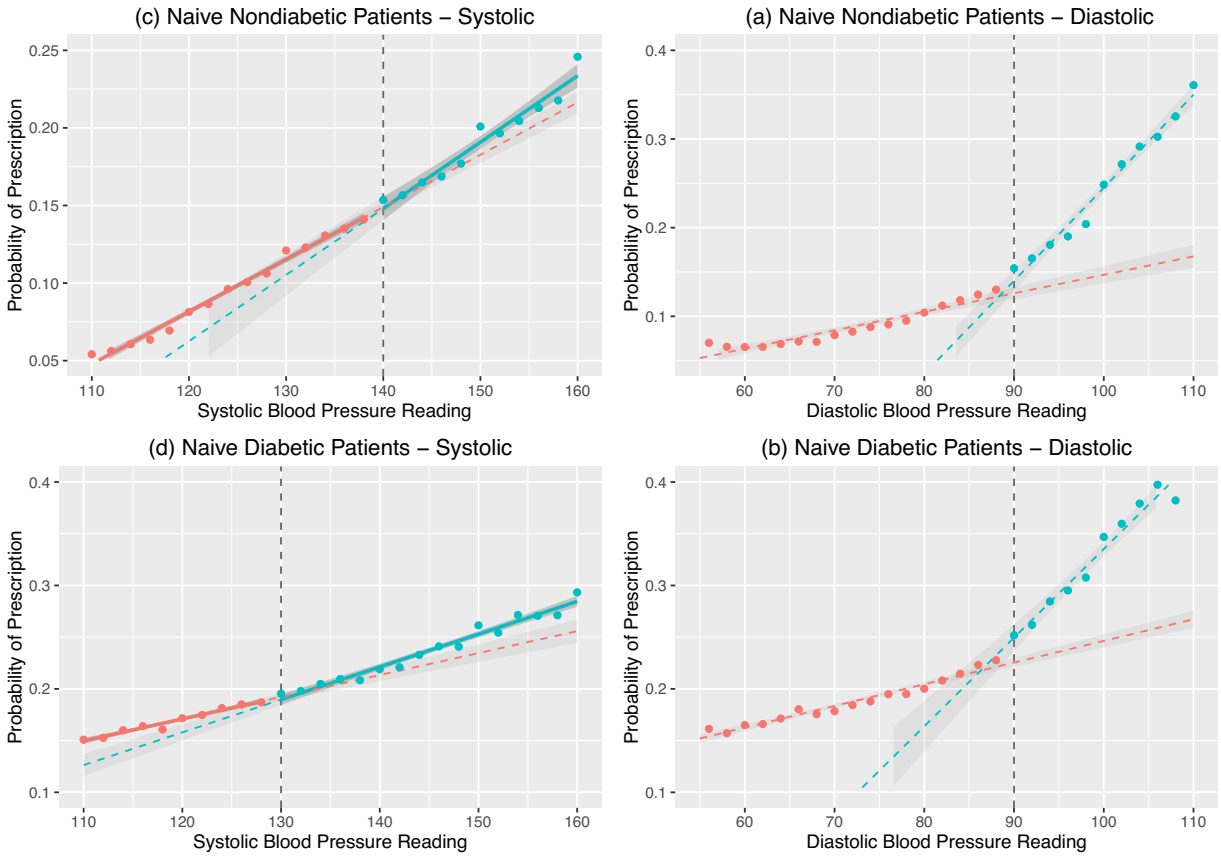


Table 3.3: Predicted Probability of Prescription conditional on Blood Pressure Reading During Office Visit (Race, Gender, Health Status, Age)

		Race			Gender		Health		Age						
SBP Range (mmHg)	All Patients	White	Black	Asian	Male	Female	Comorbid	Healthy	18-30	30-40	40-50	50-60	60-70	70-80	80+
100-104	4.9%	4.7%	7.4%	5.6%	6.5%	4.3%	9.2%	3.8%	0.9%	2.9%	5.6%	8.0%	9.2%	8.5%	7.1%
105-109	5.7%	5.4%	8.6%	6.5%	7.3%	5.0%	10.2%	4.4%	1.0%	3.3%	6.3%	9.0%	10.2%	9.4%	7.9%
110-114	7.0%	6.6%	10.7%	9.4%	8.3%	6.3%	11.8%	5.5%	1.1%	3.8%	7.3%	10.2%	11.7%	10.8%	9.1%
115-119	8.3%	7.8%	12.6%	10.2%	9.4%	7.6%	13.2%	6.5%	1.3%	4.4%	8.4%	11.6%	13.1%	12.1%	10.1%
120-124	10.3%	9.6%	15.9%	14.0%	11.1%	9.8%	15.2%	8.2%	1.5%	5.1%	9.7%	13.3%	15.0%	13.8%	11.6%
125-129	12.2%	11.4%	18.6%	15.4%	12.8%	11.7%	17.1%	9.7%	1.7%	5.9%	11.1%	15.1%	16.8%	15.4%	12.9%
130-134	14.1%	13.0%	21.8%	19.3%	14.6%	13.8%	19.5%	11.1%	1.9%	6.5%	12.2%	16.7%	18.5%	17.0%	14.2%
135-139	15.6%	14.4%	23.7%	19.6%	16.0%	15.3%	21.0%	12.3%	2.1%	7.3%	13.5%	18.2%	20.0%	18.2%	15.2%
140-144	17.5%	16.1%	26.3%	23.3%	17.7%	17.2%	22.1%	14.3%	2.4%	8.0%	14.7%	19.7%	21.6%	19.8%	16.7%
145-149	19.2%	17.6%	28.2%	24.1%	19.4%	19.0%	24.0%	15.7%	2.7%	8.9%	16.3%	21.7%	23.6%	21.5%	18.1%
150-154	21.9%	20.0%	31.9%	28.5%	22.3%	21.6%	26.7%	18.1%	3.1%	10.3%	18.4%	24.2%	26.2%	23.9%	20.3%
155-159	23.2%	21.2%	33.2%	28.6%	23.7%	22.9%	28.1%	19.3%	3.3%	11.0%	19.6%	25.5%	27.6%	25.1%	21.2%
160-164	25.9%	23.6%	36.8%	32.6%	26.5%	25.4%	30.7%	21.7%	3.7%	12.6%	21.8%	28.2%	30.2%	27.5%	23.4%
165-169	26.7%	24.2%	37.5%	33.0%	27.5%	26.2%	31.4%	22.3%	3.8%	12.9%	22.7%	29.0%	31.1%	28.1%	23.8%
170-174	29.9%	27.2%	41.3%	36.5%	30.8%	29.4%	34.7%	25.3%	4.5%	15.1%	25.7%	32.5%	34.4%	31.2%	26.7%
175-179	30.3%	27.4%	41.3%	34.9%	31.3%	29.7%	34.7%	25.5%	4.8%	15.3%	26.1%	32.8%	34.8%	31.5%	26.6%
180-184	33.7%	30.5%	45.2%	39.8%	34.7%	33.1%	38.3%	28.7%	5.6%	18.1%	29.3%	36.6%	38.4%	34.9%	29.7%
185-189	33.4%	29.9%	44.8%	39.3%	34.5%	32.8%	37.8%	28.2%	5.2%	17.3%	29.1%	36.3%	38.3%	34.6%	29.5%
190-194	36.6%	33.0%	48.4%	41.6%	37.9%	35.9%	41.1%	31.3%	6.3%	20.4%	32.0%	39.6%	41.5%	37.7%	32.3%
195-199	36.0%	31.9%	47.4%	39.3%	37.5%	35.2%	40.5%	30.7%	5.9%	19.8%	31.0%	39.1%	40.9%	37.1%	31.6%

Table 3.4: Predicted Probability of Prescription Conditional on Blood Pressure Reading During Office Visit (Race-Gender Combination)

SBP Range (mmHg)	All Patients	White Male	Black Male	Asian Male	White Female	Black Female	Asian Female
100-104	4.9%	6.3%	10.7%	7.5%	4.1%	6.5%	5.0%
105-109	5.7%	6.9%	11.8%	8.1%	4.7%	7.5%	5.8%
110-114	7.0%	7.9%	13.4%	11.0%	5.9%	9.7%	8.4%
115-119	8.3%	9.0%	14.9%	11.1%	7.1%	11.6%	9.6%
120-124	10.3%	10.5%	17.8%	14.8%	9.0%	15.0%	13.4%
125-129	12.2%	12.1%	20.2%	15.7%	10.8%	17.7%	15.1%
130-134	14.1%	13.7%	23.0%	19.9%	12.5%	21.1%	18.8%
135-139	15.6%	15.0%	24.8%	19.7%	13.9%	23.0%	19.6%
140-144	17.5%	16.6%	27.1%	23.8%	15.6%	25.8%	22.8%
145-149	19.2%	18.2%	29.0%	24.3%	17.1%	27.7%	23.9%
150-154	21.9%	20.7%	32.7%	29.3%	19.5%	31.4%	27.8%
155-159	23.2%	22.0%	34.1%	29.4%	20.6%	32.7%	28.0%
160-164	25.9%	24.5%	37.9%	33.6%	22.9%	36.2%	31.9%
165-169	26.7%	25.3%	38.6%	34.2%	23.4%	36.9%	32.2%
170-174	29.9%	28.4%	42.5%	37.6%	26.3%	40.7%	35.8%
175-179	30.3%	28.8%	42.5%	35.0%	26.6%	40.7%	34.8%
180-184	33.7%	31.9%	46.2%	41.7%	29.6%	44.7%	39.0%
185-189	33.4%	31.4%	46.1%	40.6%	29.1%	44.3%	38.4%
190-194	36.6%	34.5%	49.9%	41.8%	32.1%	47.6%	41.5%
195-199	36.0%	33.8%	48.0%	38.9%	30.9%	47.1%	39.7%

Within the overall analysis, females have lower odds of treatment than males (OR = 0.89±0.00). With the exception of Native Americans (OR = 0.89±0.02), White patients have the lowest odds of treatment versus their Black, Asian and Hawaiian/Pacific Island counterparts (OR = 1.95±0.00, 1.54±0.01, and 1.23±0.02) respectively).

Patients receiving care from a physician have greater odds of treatment than those treated by non-physicians such as nurses, nurse practitioners and physician assistants (OR = 1.11±0.01).

Consistently, patients with comorbid conditions have higher odds of treatment (OR = 1.43±0.00) than their otherwise healthy counterparts.

Table 3.5: Subgroup Analysis Model Results (Threshold Analysis)

	SBP Threshold Analysis (135mmHg-144mmHg)		DBP Threshold Analysis (86mmHg - 92mmHg)	
Sample Size	1,551,964		1,360,864	
	Estimate	SE	Estimate	SE
(Intercept)	0.00	0.59	0.03	0.40
Systolic BP (mmHg)	1.02	0.00		
Diastolic BP (mmHg)			1.00	0.00
Treatment Eligible	7.75	0.63	0.83	0.43
Even Systolic BP Reading				
Even Diastolic BP Reading				
Physician	1.14	0.01	1.11	0.01
Gender				
Male	1.00			
Female	0.93	0.00	0.89	0.00
Race				
White	1.00			
Black	1.91	0.01	1.96	0.01
Asian	1.66	0.02	1.47	0.02
Native American	0.90	0.04	0.92	0.04
Hawaiian / Pacific Islander	1.18	0.05	1.23	0.05
Unknown	1.17	0.01	1.17	0.01
Not Entered	1.02	0.01	1.07	0.01
Ethnicity				
Non-Hispanic	1.00			
Hispanic	1.52	0.01	1.38	0.01
Unknown	0.87	0.01	0.89	0.01
Not Entered	1.42	0.04	1.26	0.05
Marital Status				
Married	1.00			
Single	1.08	0.01	1.10	0.01
Widowed/Widower	1.09	0.01	1.10	0.01
Divorced	0.97	0.01	0.99	0.01
Separated	1.07	0.03	1.14	0.03
Partnered	0.85	0.17	0.61	0.18
Unknown	1.07	0.01	1.08	0.01
Not-Entered	2.53	0.44	1.42	0.41
Employment Status				
Unemployed	1.00			
Employed	0.95	0.01	0.96	0.01
Retired	0.85	0.01	0.85	0.01
Unknown	0.96	0.01	0.98	0.01
Not-Entered	0.96	0.01	0.93	0.01
Age Category				
Age 18-30	1.00			
Age 30-40	2.75	0.02	2.49	0.02
Age 40-50	4.25	0.02	4.19	0.02
Age 50-60	5.38	0.02	5.59	0.02
Age 60-70	5.88	0.02	6.35	0.02
Age 70-80	5.26	0.02	5.62	0.02
Age 80+	4.34	0.02	4.71	0.02
Comorbidities				
True	1.25	0.00	1.39	0.01
Interaction	1.00			
Systolic BP (mmHg) * Treatment Eligible	0.99	0.00	1.01	0.00

Threshold Analysis

To focus on the effect of the 140mmHg threshold for eligibility for treatment, we undertook an analysis using only those patients with systolic blood pressure readings in the range 135mmHg to 144mmHg (Table 3.5). We controlled for systolic blood pressure by including it as a numeric independent variable in our regression. As was the case with all other analyses, patients in this subgroup analysis with systolic blood pressure 135mmHg – 139mmHg were classified as "not guideline eligible" if in addition their diastolic blood pressure did not warrant treatment (i.e. it was less than 90mmHg) and they were not diabetic (for whom a 130mmHg threshold for treatment applies). All patients with readings of 140mmHg – 144mmHg were classified as "guideline eligible" for treatment. The results of this threshold analysis are shown in Table 3.5, and Figures 3.3(a), 3.3(b), 3.3(c) & 3.3(d).

In this analysis, we see much higher odds of treatment (OR = 7.75±0.63) among patients who are guideline eligible for treatment compared to those who are not.

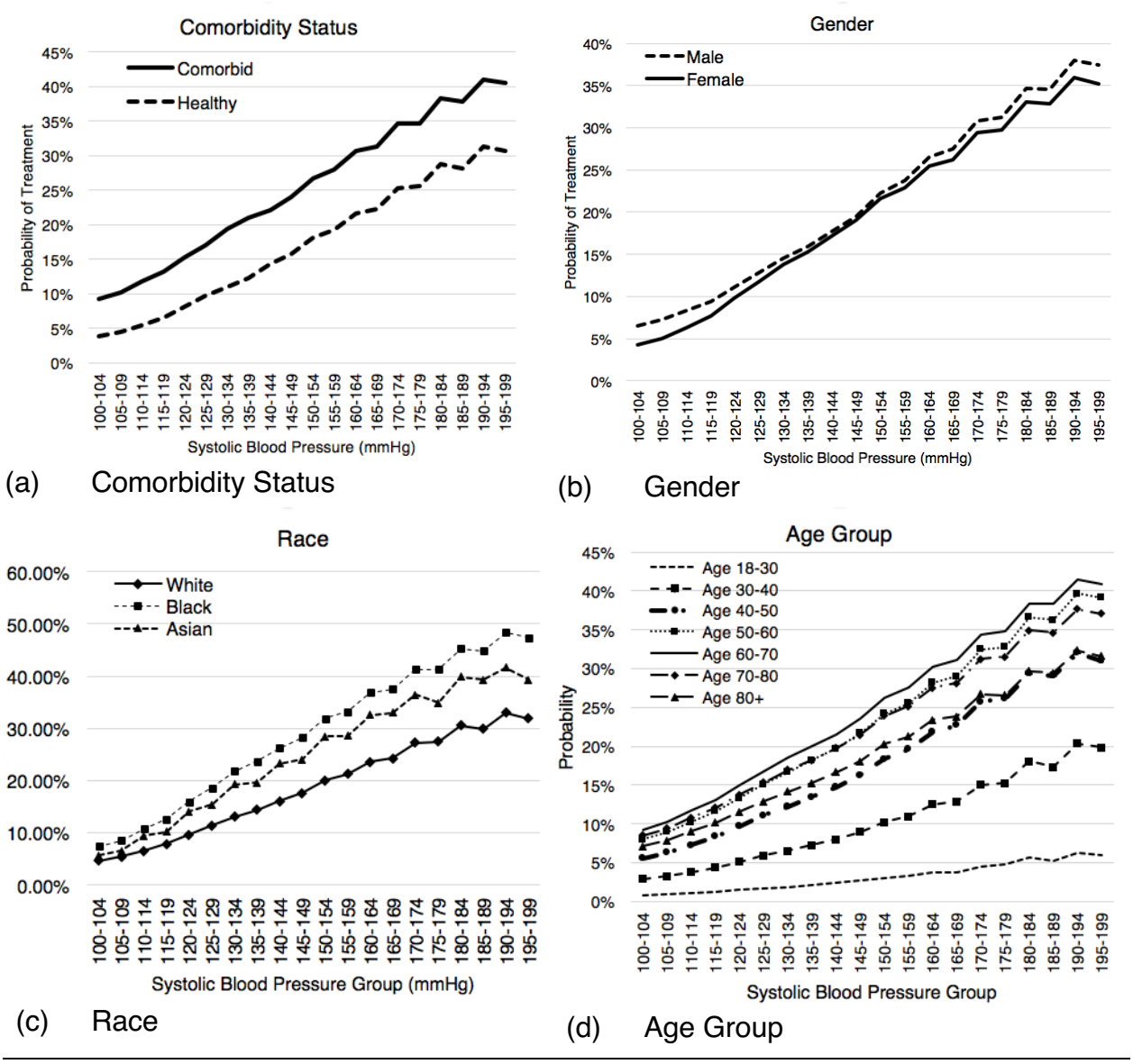
Table 3.6: Subgroup Analysis Model Results (Age)

	18-30yo		30-40yo		40-50yo		50-60yo		60-70yo		70-80yo		80+	
Sample Size	n=1,439,713		n=1,374,048		n=1,888,038		n=2,386,882		n=2,208,894		n=1,535,454		n=966,722	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
(Intercept)	0.00	0.14	0.00	0.08	0.00	0.05	0.01	0.04	0.02	0.04	0.03	0.05	0.02	0.06
Systolic BP (mmHg)	1.05	0.00	1.05	0.00	1.03	0.00	1.02	0.00	1.02	0.00	1.01	0.00	1.01	0.00
Diastolic BP (mmHg)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Treatment Eligible	10.2	0.18	5.63	0.10	2.06	0.06	1.38	0.05	1.23	0.05	1.31	0.06	1.36	0.07
Even SBP Reading	1.23	0.02	1.09	0.01	1.05	0.01	1.01	0.01	1.01	0.01	1.05	0.01	1.11	0.01
Physician	1.09	0.03	1.08	0.02	1.08	0.01	1.06	0.01	1.11	0.01	1.19	0.01	1.25	0.02
Gender														
Male	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Female	0.67	0.01	0.72	0.01	0.77	0.00	0.85	0.00	0.95	0.00	1.05	0.00	1.21	0.01
Race														
White	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Black	1.93	0.02	2.12	0.01	1.99	0.01	1.92	0.01	1.82	0.01	1.88	0.01	1.98	0.01
Asian	0.96	0.07	1.02	0.03	1.21	0.02	1.43	0.01	1.51	0.01	2.02	0.02	2.32	0.02
Native American	0.82	0.10	0.76	0.06	0.89	0.04	0.87	0.03	0.86	0.03	1.00	0.04	1.14	0.07
Hawaiian / PI	0.75	0.14	1.23	0.07	1.15	0.05	1.18	0.04	1.24	0.04	1.15	0.06	1.56	0.10
Unknown	0.92	0.02	1.05	0.01	1.12	0.01	1.19	0.01	1.27	0.01	1.32	0.01	1.22	0.01
Not Entered	0.97	0.04	0.97	0.02	0.99	0.01	1.00	0.01	1.07	0.01	1.09	0.01	1.12	0.02
Ethnicity														
Non-Hispanic	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Hispanic	1.13	0.03	1.19	0.01	1.27	0.01	1.42	0.01	1.49	0.01	1.61	0.01	1.77	0.02
Unknown	0.88	0.02	0.89	0.01	0.86	0.01	0.85	0.01	0.84	0.01	0.81	0.01	0.82	0.01
Not Entered	0.88	0.15	1.07	0.08	1.05	0.05	1.26	0.04	1.38	0.04	1.57	0.04	1.50	0.06
Marital Status														
Married	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Single	0.81	0.02	1.07	0.01	1.05	0.01	1.06	0.00	1.09	0.01	1.11	0.01	1.18	0.01
Widowed/Widower	0.99	0.28	1.10	0.07	1.08	0.03	1.04	0.01	1.07	0.01	1.07	0.01	1.08	0.01
Divorced	1.09	0.06	1.06	0.02	0.98	0.01	0.96	0.01	0.97	0.01	0.96	0.01	1.04	0.02
Separated	1.15	0.10	1.07	0.04	1.05	0.02	1.06	0.02	1.09	0.02	1.22	0.03	1.22	0.04
Partnered	0.99	0.28	0.84	0.19	0.63	0.15	0.82	0.13	1.04	0.18	1.81	0.29	0.00	19.0
Unknown	0.87	0.02	1.09	0.01	1.05	0.01	1.05	0.01	1.05	0.01	1.07	0.01	1.11	0.01
Not-Entered	1.18	0.47	2.68	0.36	1.32	0.49	1.22	0.32	1.11	0.46	2.77	0.71		
Employment Status														
Unemployed	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Employed	0.88	0.03	0.94	0.02	1.01	0.01	1.01	0.01	0.91	0.01	0.88	0.02	0.96	0.03
Retired	1.75	0.28	1.02	0.11	0.96	0.04	0.93	0.01	0.83	0.01	0.77	0.02	0.75	0.02
Unknown	0.95	0.02	1.00	0.01	1.01	0.01	1.00	0.01	0.91	0.01	0.86	0.02	0.87	0.02
Not-Entered	0.83	0.03	0.93	0.02	0.91	0.01	0.93	0.01	0.91	0.01	0.94	0.02	1.00	0.03
Comorbidities														
False	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
True	4.05	0.02	2.61	0.01	1.98	0.01	1.57	0.00	1.30	0.00	1.14	0.00	1.07	0.01
Interaction														
Systolic BP (mmHg)* Treatment Eligible	0.99	0.00	0.99	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00

Subgroup Analyses

We conducted subgroup analyses by age, gender and comorbidity status. Results of these analyses are shown in Tables 3.6 & 3.7 and Figures 3.4(a)-(d), and discussed in the following text.

Figure 3.4(a) – (d): Charts showing predicted probability of prescription by subgroup



Within our subgroup analyses stark differences are evident in treatment probabilities for different age groups. Patients age 60-69 who satisfy the JNC7 guidelines are much more likely than their 18-30-year-old counterparts to receive any medication for their hypertension (OR = 10.83±0.01). Indeed, treatment is more likely at higher ages, with all age groups having odds of treatment between 3.5 and 10.8 compared to the 18-30-year age group.

Marital status also affects treatment. Persons describing themselves as "partnered", that is, living as a married couple yet not married, have divergent odds of treatment based upon comorbidity status. Comorbid "partnered" patients have odds of 1.35 versus their healthier "partnered" counterparts, whose odds are 0.617. Patients who are classified as having comorbidities have much lower odds of treatment than their otherwise healthy counterparts based on guideline criteria alone.

The effect of the JNC7 guideline eligibility for treatment on odds of treatment initiation for comorbid patients is 0.80±0.04, compared to odds of 6.85±0.03 for those with none of the six comorbidities.

Table 3.7: Subgroup Analysis Model Results (Gender, Health Status)

	Female Only		**Male Only**		**Without Comorbidities**		**With Comorbidities**	
Sample Size	n=7,020,125		n=4,779,626		n=7,935,140		n=3,864,611	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE
(Intercept)	0.00	0.03	0.00	0.03	0.00	0.02	0.01	0.03
Systolic BP (mmHg)	1.03	0.00	1.02	0.00	1.03	0.00	1.01	0.00
Diastolic BP (mmHg)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Treatment Eligible	4.79	0.03	1.22	0.04	6.85	0.03	0.80	0.03
Even Systolic BP Reading	1.03	0.00	1.04	0.00	1.08	0.00	1.01	0.00
Even Diastolic BP Reading								
Physician	1.10	0.01	1.11	0.01	1.12	0.01	1.11	0.01
Gender								
Male					1.00		1.00	
Female					0.85	0.00	0.95	0.00

Race								
White	1.00		1.00		1.00		1.00	
Black	2.05	0.00	1.84	0.00	2.12	0.00	1.78	0.00
Asian	1.55	0.01	1.52	0.01	1.39	0.01	1.71	0.01
Native American	0.86	0.02	0.95	0.02	0.92	0.02	0.86	0.02
Hawaiian / Pacific Islander	1.22	0.03	1.22	0.03	1.14	0.03	1.28	0.03
Unknown	1.25	0.00	1.16	0.00	1.17	0.00	1.27	0.00
Not Entered	1.04	0.01	1.05	0.01	1.07	0.01	1.03	0.01
Ethnicity								
Non-Hispanic	1.00		1.00		1.00		1.00	
Hispanic	1.41	0.00	1.41	0.01	1.23	0.01	1.56	0.01
Unknown	0.83	0.00	0.85	0.00	0.83	0.00	0.85	0.00
Not Entered	1.33	0.02	1.29	0.03	1.30	0.03	1.33	0.02
Marital Status								
Married	1.00		1.00		1.00		1.00	
Single	1.10	0.00	1.07	0.00	1.06	0.00	1.11	0.00
Widowed/Widower	1.06	0.00	1.01	0.01	1.11	0.01	1.08	0.00
Divorced	0.97	0.00	1.01	0.01	1.01	0.01	0.96	0.01
Separated	1.11	0.01	1.08	0.02	1.07	0.02	1.12	0.01
Partnered	1.24	0.10	0.58	0.10	0.62	0.10	1.35	0.11
Unknown	1.08	0.00	1.04	0.00	1.05	0.00	1.10	0.00
Not-Entered	1.52	0.21	1.82	0.31	1.35	0.24	1.69	0.25
Employment Status								
Unemployed	1.00		1.00		1.00		1.00	
Employed	0.91	0.01	0.99	0.01	0.97	0.01	0.99	0.01
Retired	0.81	0.01	0.84	0.01	0.88	0.01	0.83	0.01
Unknown	0.93	0.00	0.95	0.01	0.98	0.01	0.95	0.01
Not-Entered	0.92	0.01	0.95	0.01	0.94	0.01	0.96	0.01
Age Category								
Age 18-30	1.00		1.00		1.00		1.00	
Age 30-40	3.84	0.01	3.08	0.01	3.33	0.01	2.01	0.02
Age 40-50	7.92	0.01	5.51	0.01	6.47	0.01	2.83	0.02
Age 50-60	11.90	0.01	7.20	0.01	9.59	0.01	3.31	0.02
Age 60-70	14.38	0.01	7.56	0.01	11.76	0.01	3.40	0.02
Age 70-80	13.39	0.01	6.37	0.01	11.29	0.01	2.93	0.02
Age 80+	11.43	0.01	4.71	0.01	9.66	0.01	2.35	0.02
Comorbidities								
True	1.43	0.00	1.45	0.00				
Interactions								
Systolic BP (mmHg) *								
Treatment Eligible	0.99	0.00	1.00	0.00	0.99	0.00	1.00	0.00

Discussion

Our analyses show that physician behavior appears to be influenced by the JNC7 guidelines. Patients who satisfy the guidelines are more likely to receive a prescription for a suitable medication than similar patients who do not.

Despite the positive effect of SBP on treatment initiation, many patients with elevated blood pressure readings are not receiving recommended treatment. More

specifically, patients satisfying the criteria for treatment specified in the JNC7 Guidelines are only prescribed an antihypertensive medication between 17% (systolic blood pressure category 140mmHg – 144mmHg) and 36% (systolic blood pressure category 195mmHg – 199mmHg) of the time. It is unclear whether there are clinical reasons for this deviation, and if so what those reasons might be, but it nonetheless seems likely that a significant portion of eligible patients are left untreated for reasons unrelated to their clinical parameters. In short, our results indicate significant under-treatment of hypertension for patients across all ages, races and for both men and women.

We also find that patient characteristics such as age, race and comorbidity status influence treatment probability, with younger patients much less likely to receive recommended treatment. Notably, in our data, black patients are more likely to receive treatment than their white counterparts. This finding may seem incongruent with much of the literature, because it is well known that black patients have worse outcomes for hypertension at a population level[2]. Nonetheless, among those blacks who visit their primary care doctor, our findings suggest that black patients are more likely to receive guideline-concordant care, This finding is supported by those of prior authors[7,10,11]. Perhaps the higher rates of treatment are due to physician awareness of these worse outcomes and a perception that hypertension among black patients may be more likely to be recalcitrant, conditioning physicians to treat black patients more aggressively.

Prescribing occurs more often for qualifying patients who are seen by physicians compared to those patients who are treated by non-physician healthcare specialists.

Further analysis is necessary to determine whether this is due to prescribing limitations or other factors.

We recognize that many physicians may not wish to prescribe medications to patients after a single, initial high reading due to a possible “white coat effect”, and/or a preference to try to implement lifestyle modifications with the patient before resorting to medication. While this reasoning may apply in many cases, this practice deviates from the JNC7 guidelines and the argument is inconsistent with the findings of prior studies conducted at several centers across the United States that indicate patients with repeated high blood pressure readings often remain untreated[4].

The size and geographic breadth of our sample leads us to conclude that our findings apply broadly, not to just some niche populations, and that the phenomenon of undertreatment of hypertension is widespread. Thus, this represents a large opportunity for major improvements in cardiovascular primary and specialty care. While patient non-adherence to medications is often an issue, our analysis specifically focuses on medical practitioner behavior and clinicians’ adherence to guidelines. A large gap exists between recommended care and that which is being applied in actual practice.

Surprisingly, in a model with DBP and age controls our analysis indicates a mild negative association of diastolic blood pressure on treatment initiation. Why this is so is unclear, but it could relate to a positive correlation (~0.3) between age and SBP and a slight negative correlation between age and DBP (~ -0.04). Older patients typically exhibit higher systolic blood pressure. Thus, if physicians are more likely to initiate therapy based upon systolic blood pressure the age-SBP correlation may manifest itself

as a positive effect of age on treatment initiation in models with no SBP covariate and mask a smaller effect of diastolic blood pressure on treatment initiation.

This study utilizes electronic medical records. Therefore it is therefore subject to the limitations of data collected for clinical use rather than research. It is possible that some medications prescribed were not recorded in the electronic records system. We are also unable to determine whether physicians were choosing not to prescribe due to patient requests for lifestyle modifications, or due to referral to other providers, or for other reasons that may be clinically viable, yet at variance with JNC7 expectations.

Conclusion

This study was initiated to assess the effectiveness of the JNC7 guidelines for hypertension treatment. That investigation revealed an important finding that was not part of our initial motivation. There is substantial under-treatment for hypertension. Nearly two-thirds of tested patients for whom the guidelines recommend treatment did not receive it. Moreover, 31.8% had guideline eligible blood pressures, and 11.9% of our sample had blood pressures that were more than ten points above the level where treatment is recommended.

To return to our initial purpose, for patients without any prior pharmacologic treatment for hypertension the JNC7 guidelines are associated with increases in physician hypertension drug prescribing behavior. This effect varies by age, race and comorbidity status.

In short, there is evidence that the JNC7 guidelines have an effect, but the effect falls far short of getting the vast majority of patients who need treatment to receive treatment.

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Appendix 1 – Supplementary Materials for Chapter 1

Supplementary Table 1.1 – Complication Rates for Repeat Biopsy

Supplementary Table 1: Complication Rates for Repeat Biopsy

Biopsy Number	Complication Rate (per biopsy)
1	0.02
2	0.02
3	0.055
4	0.1
5	0.15
6	0.16
7	0.12

Economic Model Literature Review Search Terms and Findings

Search Terms:

("prostate"[Title] OR "prostatic"[Title]) AND (("neoplasms"[MeSH Terms] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields])) AND ("Economic Model"[Title/Abstract] OR "Decision Model"[Title/Abstract] OR "Decision Tree"[Title/Abstract] OR "Health Economic"[Title/Abstract] OR "Markov"[Title/Abstract] OR "Cost-Effectiveness"[Title/Abstract] OR "Cost-Utility"[Title/Abstract]) AND ("2003/12/12"[PDAT] : "2014/12/08"[PDAT])

Relevant Publications from the search are shown below:

1: Huguet J, Musquera M, Ribal MJ, Alcaraz A. [Economic features of active surveillance]. Arch Esp Urol. 2014 Jun;67(5):509-13. Spanish. PubMed PMID: 24914850.

2: Koerber F, Waidelich R, Stollenwerk B, Rogowski W. The cost-utility of open prostatectomy compared with active surveillance in early localised prostate cancer. BMC Health Serv Res. 2014 Apr 10;14:163. doi: 10.1186/1472-6963-14-163. PubMed PMID: 24721557; PubMed Central PMCID: PMC4022451.

3: Dragomir A, Cury FL, Aprikian AG. Active surveillance for low-risk prostate cancer compared with immediate treatment: a Canadian cost comparison. CMAJ Open. 2014 Apr 24;2(2):E60-8. doi: 10.9778/cmajo.20130037. eCollection 2014 Apr. PubMed PMID: 25077131; PubMed Central PMCID: PMC4084746.

4: Bolenz C, Freedland SJ, Hollenbeck BK, Lotan Y, Lowrance WT, Nelson JB, Hu JC. Costs of radical prostatectomy for prostate cancer: a systematic review. Eur Urol. 2014 Feb;65(2):316-24. doi: 10.1016/j.eururo.2012.08.059. Epub 2012 Sep 5. Review. PubMed PMID: 22981673.

5: Close A, Robertson C, Rushton S, Shirley M, Vale L, Ramsay C, Pickard R. Comparative cost-effectiveness of robot-assisted and standard laparoscopic prostatectomy as alternatives to open radical prostatectomy for treatment of men with localised prostate cancer: a health technology assessment from the perspective of the UK National Health Service. Eur Urol. 2013 Sep;64(3):361-9. doi: 10.1016/j.eururo.2013.02.040. Epub 2013 Mar 7. PubMed PMID: 23498062.

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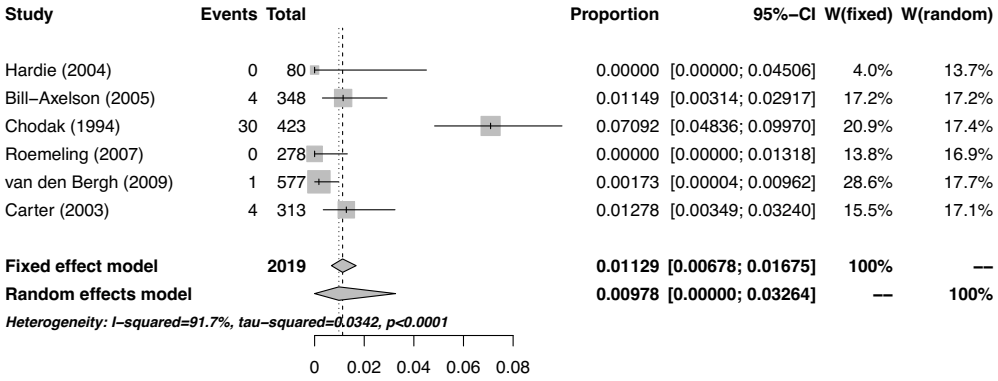
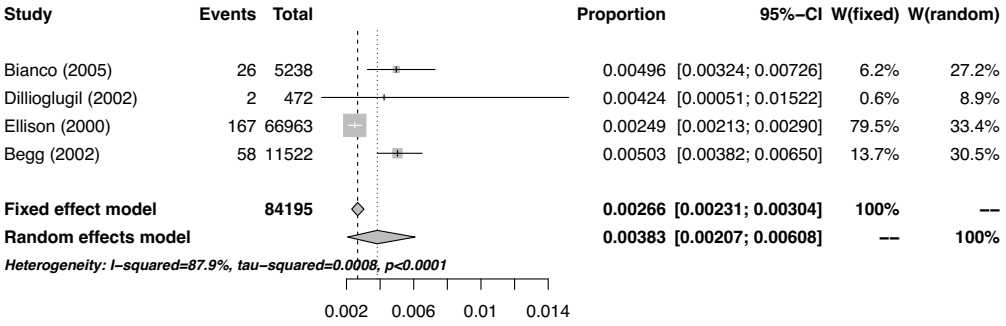
Supplementary Figure 1.1 – Meta-Analysis (Metastases)

Supplementary Figure 1. Meta-analysis of probability of occurrence of metastases before treatment

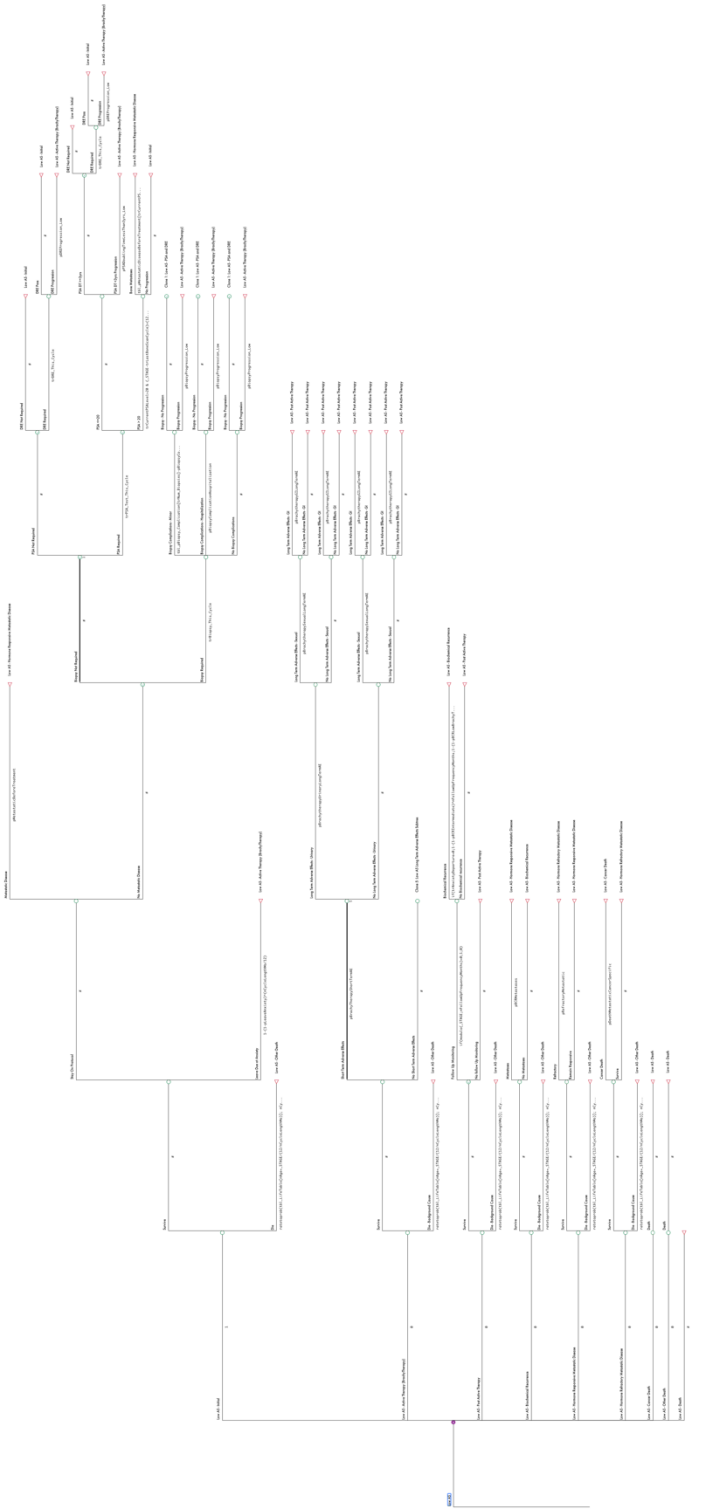


Supplementary Figure 1.2 – Meta-Analysis (Mortality)

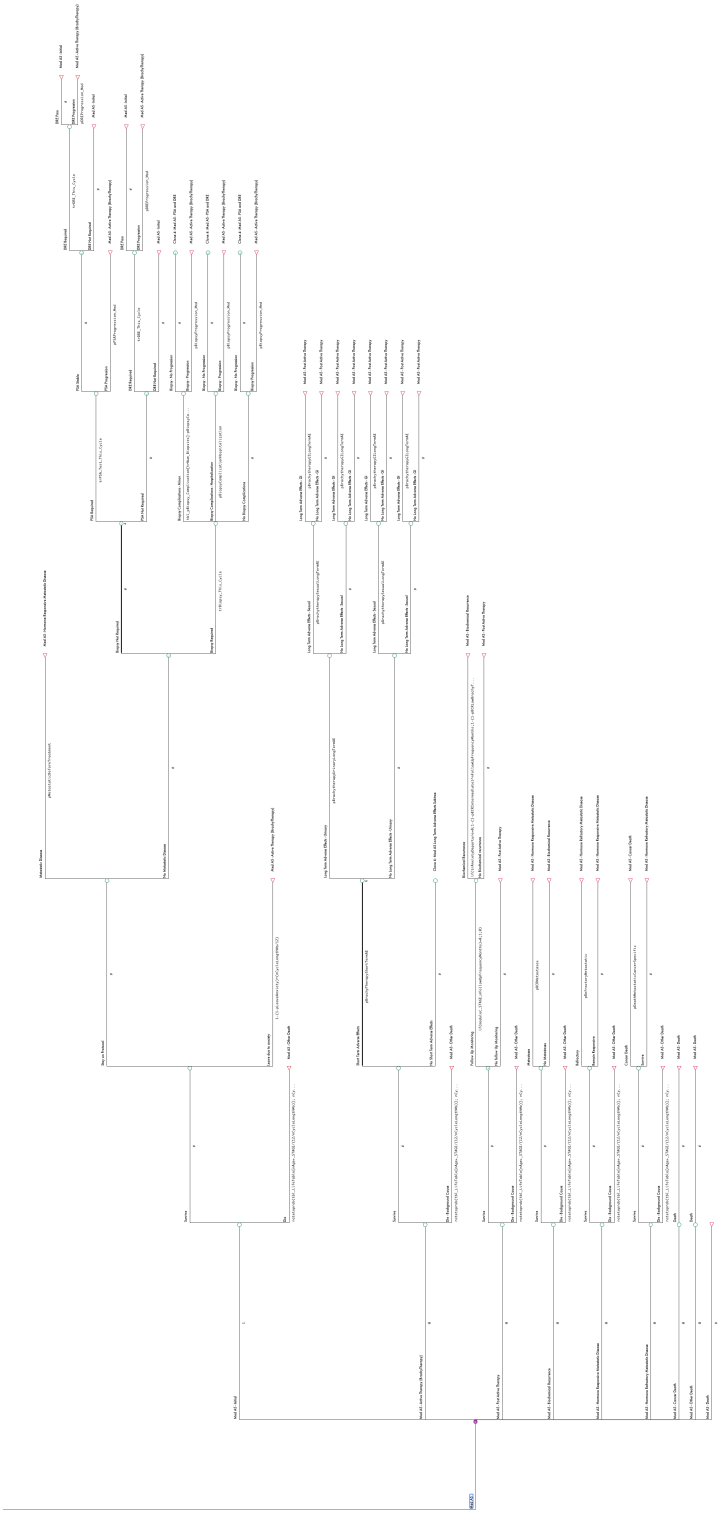
Supplementary Figure 2: Meta-analysis of probability of perioperative (30-day) death due to prostatectomy



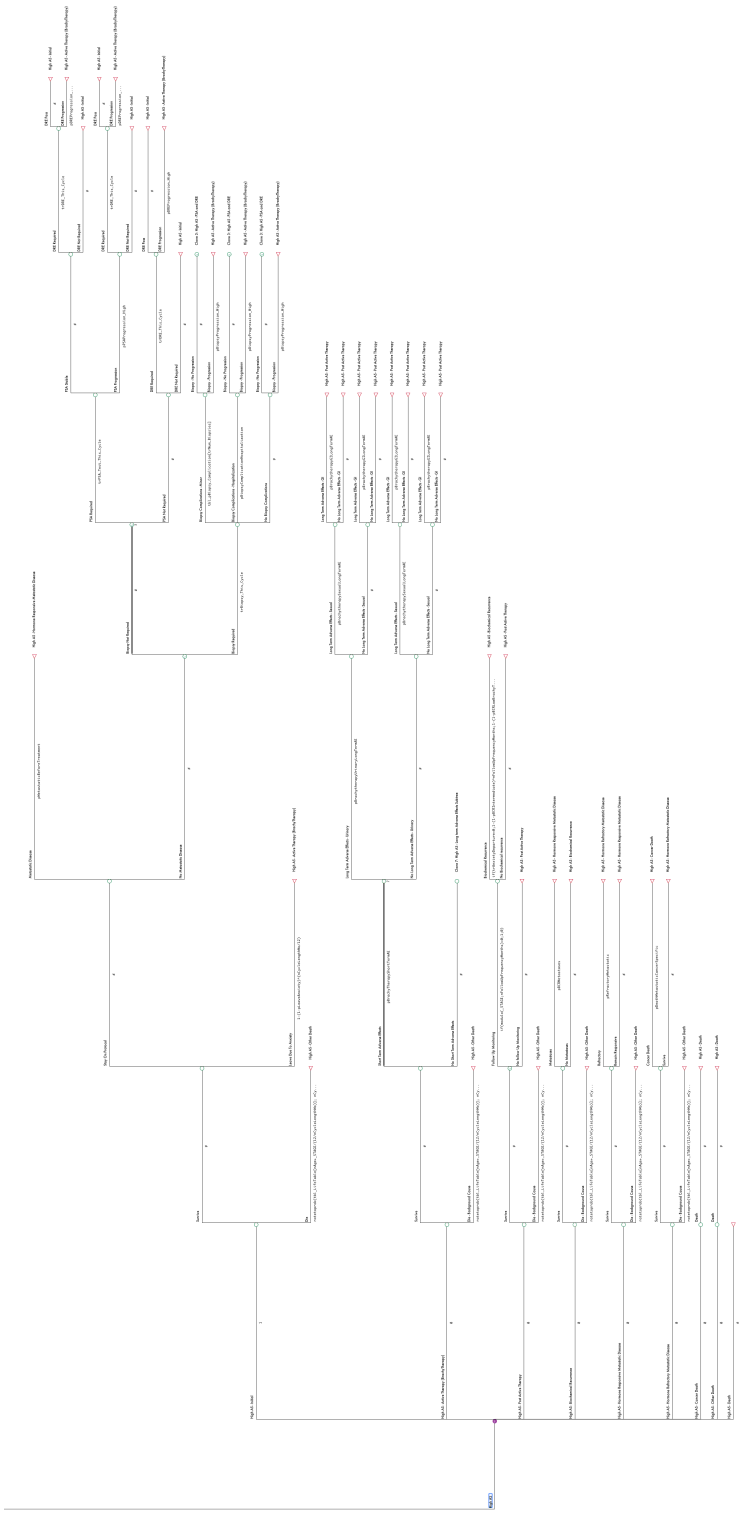
Supplementary Figure 1.3 – Model Structure (Low-intensity AS Strategy)



Supplementary Figure 1.4 – Model Structure (Medium-intensity AS Strategy)



Supplementary Figure 1.5 – Model Structure (High-intensity AS Strategy)



Supplementary Figure 1.6 – Model Structure (Immediate Treatment Strategy)

Appendix 2 – Supplementary Materials for Chapter 2

Thyroid Model – Natural History Models

Data Source

Data for the analysis was provided by Dr Akira Miyauchi and Dr Yasuhiro Ito from Kuma Hospital in Japan over the period 1996 to the present.

The dataset consists of patients with Thyroid nodules. Patients have elected not to undergo treatment, and are monitored via regular ultrasound evaluations during which the size of the nodule is measured by the physician.

Nodule sizes are measured in mm, usually to the nearest whole number mm. Patient characteristics such as gender, date of birth, family history of cancer, history of radiation exposure, multifocality of the thyroid nodule(s), presence of lymph node metastases etc… are collected.

For each patient multiple readings are contained in the dataset. The data format is wide, with each row containing readings for multiple dates.

Data Cleansing

Data cleansing was undertaken in SQL Server and R. Data from the file "160515_Ito_Lubitz_microPTC_FINAL.xlsx" was used for the final analysis of patient histories.

A multiple stage import was undertaken:

1) Import the Excel file using the SQL server data import tool. Select only the worksheet called 'Sheet1' for import. The first row of the file is used for headers. Import it into a table called "Lubitz_PTMC_Data_Simple_New"

2) Run the following SQL Code to import and convert the data structure to a long format for analysis and create a new table called “PTMC_DATA_CLEAN”

```
/** Script to manipulate the Ito Data into R required format for Gompertz Model      **/
/* Change the row based format into columns so that R can import it for NLS model     */
/* Works for up to 27 readings, add more rows in the union to accommodate more       */
/* readings when modeling for the distribution, pay attention to serial correlation   */
DROP TABLE PTMC_Data.dbo.PTMC_DATA_CLEAN
select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF, DO_US_0 as
Reading_Date, Size_0 as Size, 0 as Time_Elapsed INTO
PTMC_Data.dbo.PTMC_DATA_CLEAN from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New
as PTMC
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_1 as Reading_Date, Size_1 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_1 as DATE)) as Time_Elapsed from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_1
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_2 as Reading_Date, Size_2 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_2 as DATE))  from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as
PTMC_2
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_3 as Reading_Date, Size_3 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_3 as DATE))  from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as
PTMC_3
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_4 as Reading_Date, Size_4 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_4 as DATE))  from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as
PTMC_4
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_5 as Reading_Date, Size_5 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_5 as DATE))  from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as
PTMC_5
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_6 as Reading_Date, Size_6 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_6 as DATE))  from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as
PTMC_6
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
```

```
DO_US_7 as Reading_Date, Size_7 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_7 as DATE))  from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as
PTMC_7
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_8 as Reading_Date, Size_8 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_8 as DATE))  from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as
PTMC_8
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_9 as Reading_Date, Size_9 as Size, DATEDIFF(day,cast(DO_US_0 as Date),
CAST(DO_US_9 as DATE))  from PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as
PTMC_9
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_10 as Reading_Date, Size_10 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_10 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_10
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_11 as Reading_Date, Size_11 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_11 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_11
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_12 as Reading_Date, Size_12 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_12 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_12
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_13 as Reading_Date, Size_13 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_13 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_13
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
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Date), CAST(DO_US_14 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_14
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_15 as Reading_Date, Size_15 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_15 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_15
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_16 as Reading_Date, Size_16 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_16 as DATE))  from
```

```
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_16
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
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Date), CAST(DO_US_17 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_17
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_18 as Reading_Date, Size_18 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_18 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_18
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
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Date), CAST(DO_US_19 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_19
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
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Date), CAST(DO_US_20 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_20
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
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Date), CAST(DO_US_21 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_21
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
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Date), CAST(DO_US_22 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_22
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_23 as Reading_Date, Size_23 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_23 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_23
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_24 as Reading_Date, Size_24 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_24 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_24
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
DO_US_25 as Reading_Date, Size_25 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_25 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_25
Union select ID, DOB, Age, Female, RadHx, FamHxPTC, Susp_LNM, Susp_MF,
```

```
DO_US_26 as Reading_Date, Size_26 as Size, DATEDIFF(day,cast(DO_US_0 as
Date), CAST(DO_US_26 as DATE))  from
PTMC_Data.dbo.Lubitz_PTMC_Data_Simple_New as PTMC_26
```

3) Remove all invalid rows and select only the columns that we want from the data by performing the following SQL select statement.

Invalid rows are those where:

- Time elapsed is NULL or negative
- Patient ID is not greater than 100
- Tumor Size is not greater than 0mm

```
/* Select only the rows that are complete. */

Select
      [ID] AS patient_id,
      [Time_Elapsed] AS Time_Elapsed,
      [Age] AS Age,
      [Female] AS Female,
      [RadHx] AS RadHx,
      [FamHxPTC] AS FamHxPTC,
      [Susp_LNM] AS Susp_LNM,
      [Susp_MF] AS Susp_MF,
      [Size] AS Tumor_Size
  FROM [PTMC_Data].[dbo].[PTMC_DATA_CLEAN]
  where time_elapsed >=0 and ID >100 AND Size > 0
  order by ID asc, time_elapsed asc
```

The data that are produced needs to be exported manually using the export feature in SQL Server. Export the full data table to a file named “PTMC Data TXT File - Clean - Unique.csv”

Growth Model Statistical Analysis

To prepare for statistical analysis, further data manipulation is required to ensure bad data are removed. The following steps have to be taken. Code provided is for R version 3.3.0 in RStudio version 0.99.896 on Mac OSX ver 10.11.2.

Pre-Analysis and Manipulation

Read Data File

```
# Data file was modified within SQL Server to drop any rows where the dates
# were the same but the tumor size was different. I decided to keep the
# largest tumor size value of the duplicates.
# Read in Data and select the patients we want to keep


PTMC <- read.csv('/PTMC Data TXT File - Clean - Unique.csv')
```

This reads in the CSV file. The file location will need to be specified for the correct location on the local machine.

Remove Bad Data

We need to remove any patients who do not meet the following criteria:

- Age ≥ 18 (0 patients removed)
- Tumor Size ≥ 4mm for all readings (0 patients removed)
- Minimum of 3 readings of tumor size (0 patients removed)

We do this via the following code:

```
#Get a list of patients who are under age 18 and drop them
bad.patients.age <- as.numeric(unique(PTMC$patient_id[(PTMC$Age <18)]))
PTMC <- PTMC[!(PTMC$patient_id %in% bad.patients.age),]
# Get a list of patients who have tumor size measurements of 0 and drop them
bad.patients.tumor_size <- as.numeric(unique(PTMC$patient_id[(PTMC$Tumor_Size <4)]))
PTMC <- PTMC[!(PTMC$patient_id %in% bad.patients.tumor_size),]

# Create the master data table with only patients who have more than 3 readings
good.patients <- as.numeric(names(table(PTMC$patient_id)))[table(PTMC$patient_id)>3]
Thyroid_Master<-PTMC[PTMC$patient_id %in% good.patients,]
```

Examine the Data for weirdness…

Next, check the data for any strange elements or features. This can be achieved through use of multiple tools. This exercise is left to the reader to undertake. Importantly though, look for empty rows, negative values (should not exist for count or size data) dates that are out of order etc…

Option 1: Analysis with Automated Exponential Model Fitting

Step 1 – Identify Patient Types

Our pre-existing hypothesis is that patients will either have tumors that grow, shrink, or remain stable. We wish to classify each patient as having either

- Growing Tumor
- Shrinking Tumor
- Stable Tumor Size

Using the TumGR package in R, we can attempt to automatically fit exponential models for each patient's data. Since each patient has at least 3 readings, this should be achievable for any monotonic patients. TumGR does not allow for the use of covariates since it is designed for use in clinical trial modeling. We will use it here not for model specification, but purely as a patient classifier.

The TumGR package also allows for the fitting of an additive growth / decay model of the form

$$Tumor\ Size = e^{g.t} + e^{-dt}$$

In this model values for g and d drive growth or decay with at least one having a strictly positive value. For a growth model, the estimate for d will be 0, and for a decay

model the estimate for g will be 0. For patients with tumors that exhibit some combination of growth and decay we should expect positive values for both g and t.

In this analysis, out of 221 patients we see that when we use p<0.05 as our model fit threshold, 62 patients exhibit growth and have growth model fits; 52 patients are fit with decay models; 15 are fit with growth and decay combination models, and 92 patients are not fit to a model due to p-value requirement.

```
#---------------------Tumor Growth Models (exponential)---------------------------------#
#---------------------------------------------------------------------------------------#
# Tumor Growth Model Fits - Does not utilize any covariates.
# Automagically identifiies growers and shrinkers.
# Need to use days in time field since it requires integer readings (I think). Doesn't work with
years
#---------------------------------------------------------------------------------------#
#---------------------------------------------------------------------------------------#
model.fit <- gdrate(TumGR_Data, pval = 0.05, plots = FALSE)
model.fit
model.gx <- model.fit$results[model.fit$results$selectedFit == "gx",]
model.dx <- model.fit$results[model.fit$results$selectedFit == "dx",]
model.not_fit <- model.fit$results[model.fit$results$selectedFit == "not fit",]
```

The following output from TumGR provides details of the model fits:

```
$models
     Group Analyzed       Type  N Percentage
1 excluded       no error data  1          0
2 excluded      yes    not fit 91         41
3 included      yes         dx 52         24
4 included      yes         gd 15          7
5 included      yes         gx 62         28

$sumstats
  Parameter   N   Median                 IQR     Mean       SD
1         g  77 0.000104 (5.6e-05, 0.000216) 0.000155 0.000137
2         d  67 0.000124 (6.9e-05, 0.000318) 0.000261 0.000311
3       phi NaN      NaN                 NaN      NaN      NaN
```

Re-fitting models with classified patient groups

With patients classified into growth, shrinkage or stable tumor classes, we can then take each patient class and model their tumor growth behavior, now with the inclusion of patient covariates. Since we know the patient IDs of the patients who exhibit tumor growth, shrinkage or stable size, we create three new datasets, with one dataset for each group of patients using the results of the call to TumGR.

```
TumGR_Data_Growers <- Thyroid_Master[Thyroid_Master$patient_id %in% model.gx$name,]
TumGR_Data_Decayers <- Thyroid_Master[Thyroid_Master$patient_id %in% model.dx$name,]
TumGR_Data_Flatliners <- Thyroid_Master[Thyroid_Master$patient_id %in% model.not_fit$name,]
```

Growth Models

We will fit patients in this class with an exponential model. Since we know each patient individually achieved a good fit via TumGR exponential modeling, we should expect a good fit here for the group using a fixed effects exponential model.

The model is of the form:

$$\ln(Tumor\ Size_i) = \beta_{0_i} + \beta_1 Time\_Elapsed_i + X_i\beta + \epsilon$$

In this case the model fit appears to be well-specified with the following simple parameters. Other parameters such as multifocality, age, gender and radiation history are significant, but make no difference to the time dependent growth factor, so for our model these are redundant. Permutations of the covariates were tried, with model specifications including all variables, combinations and the inclusion of some interaction terms not making any meaningful difference to the time-dependent tumor growth rate. Linear (not logged) nodel specifications were also tested but these:

$$\ln(Tumor\ Size_i) = \beta_{0_i} + \beta_1 Time\_Elapsed_i + \epsilon$$

The following goodness of fit checks are shown. Due to the rounded / integer nature of the data some strange patterns emerge in the residuals, but overall they appear to be well distributed and homoscedastic. The QQ plot implies normality. Overall, the patient level fixed-effects model seems to fit well.

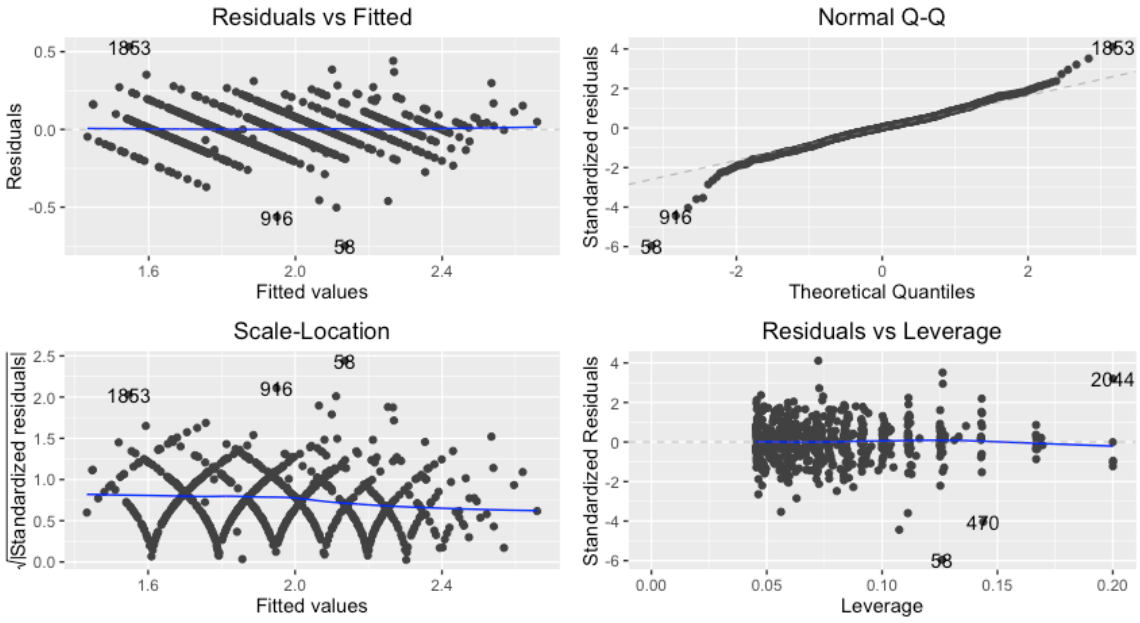
The final model specification is:

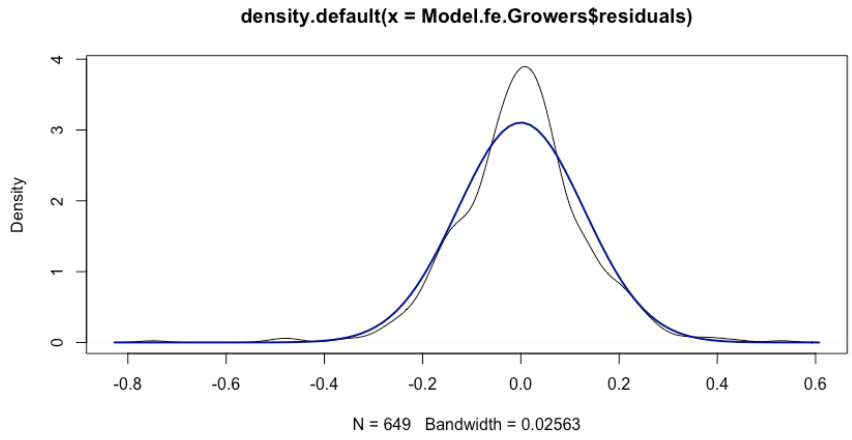
$$\ln(Tumor\ Size_i) = 1.978565 + \beta_{0_i} + 0.023598 * Time\_Elapsed_i + \epsilon$$

Where Time_Elapsed is in years and Beta_0_i is a patient level intercept / fixed effect.

Here is the results table:

```
Call:
lm(formula = log(Tumor_Size) ~ Time_Elapsed + factor(patient_id),
    data = TumGR_Data_Growers)

Residuals:
     Min       1Q   Median       3Q      Max
-0.74841 -0.07134  0.00356  0.07098  0.53198

Coefficients:
                       Estimate Std. Error t value Pr(>|t|)
(Intercept)            1.978565   0.049615  39.878  < 2e-16 ***
Time_Elapsed           0.023598   0.001568  15.050  < 2e-16 ***
factor(patient_id)102 -0.283187   0.057780  -4.901 1.23e-06 ***
factor(patient_id)103  0.219801   0.061918   3.550 0.000416 ***
… Other patient level fixed-effects intercepts removed for clarity
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.1344 on 597 degrees of freedom
Multiple R-squared:  0.7859,  Adjusted R-squared:  0.7683
F-statistic: 44.72 on 49 and 597 DF,  p-value: < 2.2e-16
```





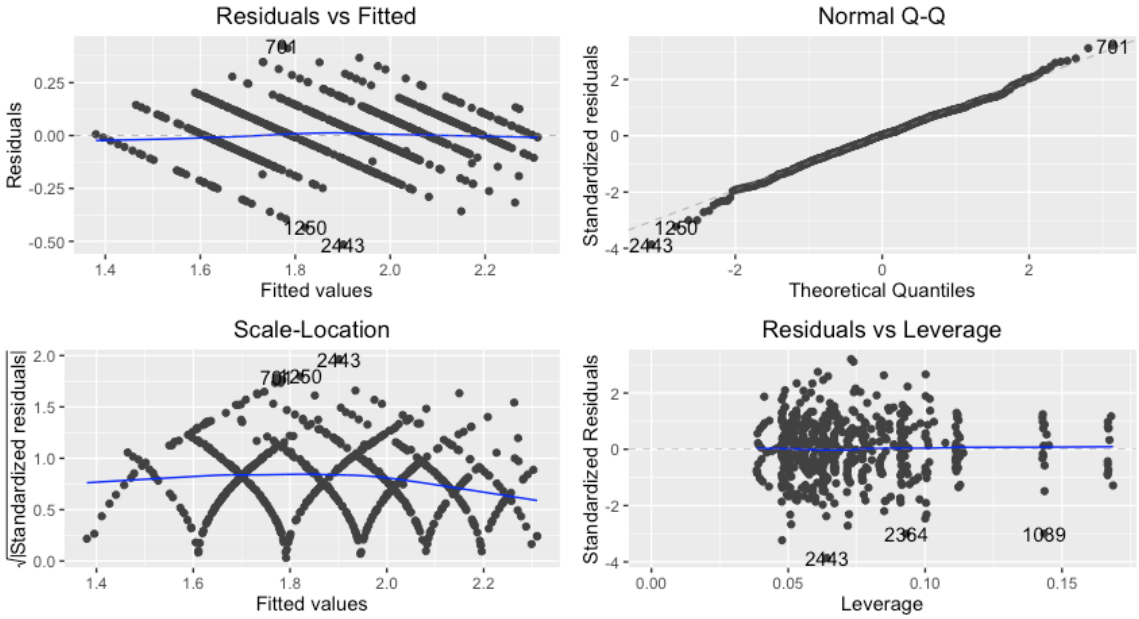
Shrinkage / Decay Models

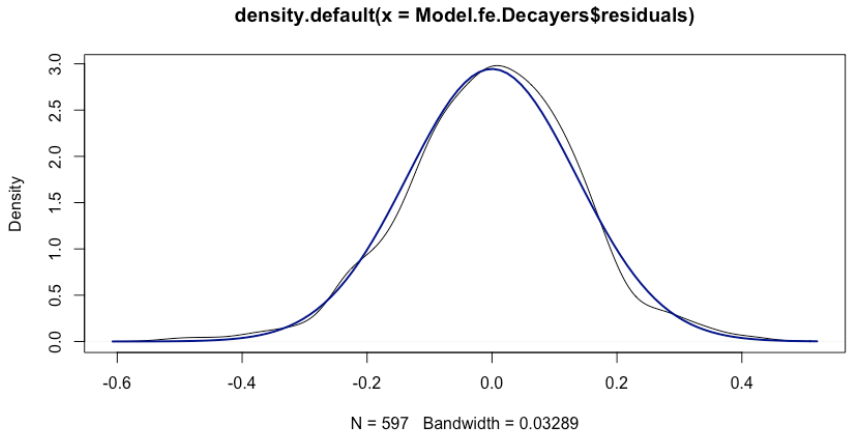
Similarly to the growth models, we utilize the classifications generated by TumGr and the test exponential model fits that determined which patients have tumors that are shrinking.

As with the growth models, the model specification is the same. The fit checks are shown, as is the summary of the model. The decay model appears to have an even better fit than the growth models.

$$\ln(Tumor\ Size_i) = 2.0499 + \beta_{0_i} - 0.015287 * Time\_Elapsed_i + \epsilon$$

```
Call:
lm(formula = log(Tumor_Size) ~ Time_Elapsed + factor(patient_id),
    data = TumGR_Data_Decayers)

Residuals:
     Min       1Q   Median       3Q      Max
-0.51459 -0.08395  0.00401  0.09149  0.42491

Coefficients:
                      Estimate Std. Error t value Pr(>|t|)
(Intercept)           2.049901   0.056485  36.291  < 2e-16 ***
Time_Elapsed         -0.015287   0.001755  -8.713  < 2e-16 ***
factor(patient_id)122  0.177187   0.067366   2.630 0.008771 **
factor(patient_id)124  0.140562   0.065246   2.154 0.031644 *
… Other patient level fixed-effects intercepts removed for clarity
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.1378 on 553 degrees of freedom
Multiple R-squared:  0.6935,  Adjusted R-squared:  0.6702
F-statistic: 29.79 on 42 and 553 DF,  p-value: < 2.2e-16
```





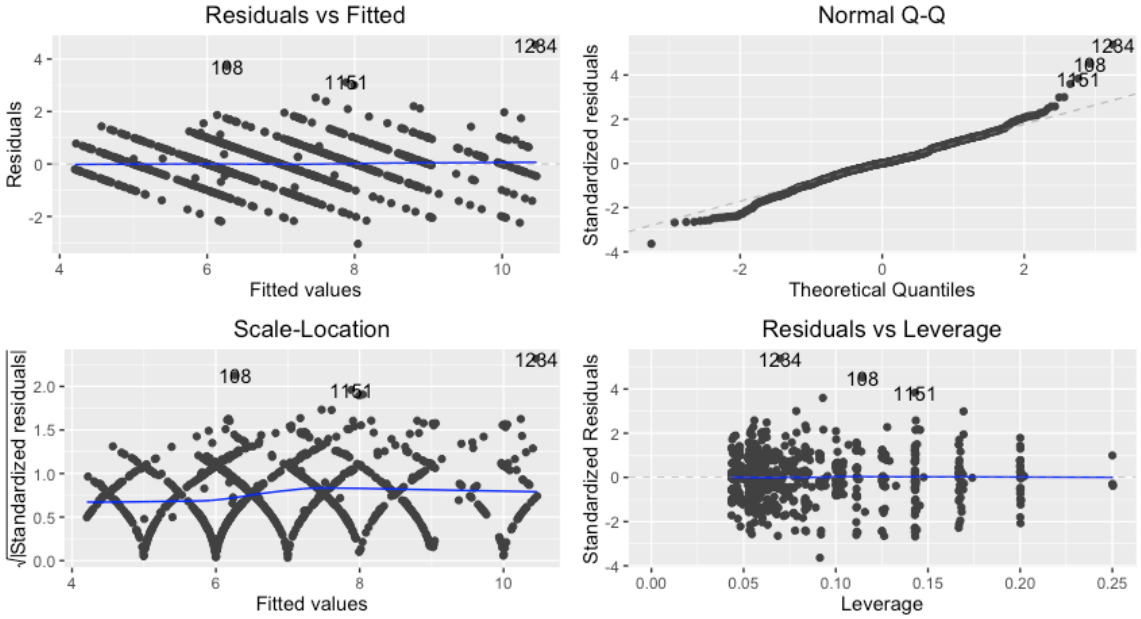
Stable Tumor Models

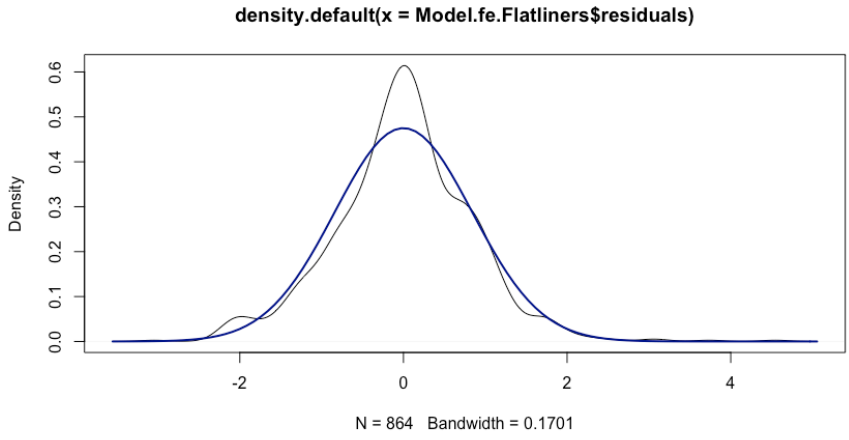
Finally, we fit the stable tumor models using untransformed linear model with patient level fixed-effects. The results of this are shown.

$$Tumor_{Size_i} = 8.44 + \beta_{0_i} + 0.0237 * Time\_Elapsed_i + \epsilon$$

```
Call:
lm(formula = (Tumor_Size) ~ Time_Elapsed + factor(patient_id),
    data = TumGR_Data_Flatliners)

Residuals:
    Min      1Q  Median      3Q     Max
-3.0438 -0.4645  0.0061  0.5145  4.5449
```

```
Coefficients:
                        Estimate Std. Error t value Pr(>|t|)
(Intercept)             8.439716   0.216115  39.052  < 2e-16 ***
Time_Elapsed            0.023684   0.009715   2.438 0.014991 *
factor(patient_id)109   1.578723   0.293124   5.386 9.51e-08 ***
factor(patient_id)110  -2.407095   0.356532  -6.751 2.83e-11 ***
… Other patient level fixed-effects intercepts removed for clarity
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.8773 on 791 degrees of freedom
Multiple R-squared:  0.7622, Adjusted R-squared:  0.7405

F-statistic:  35.2 on 72 and 791 DF,  p-value: < 2.2e-16
```





Other model types

In addition to the logged-linear models that were utilized, other models were tested. Panel data models were tested using R package plm, for panel linear models. The results of this fixed effects panel regression generated identical findings to that using patient level fixed-effects in a regular linear model, which is unsurprising. The results are shown for the growth model fit.

```
Oneway (individual) effect Within Model

Call:
plm(formula = log(Tumor_Size) ~ Time_Elapsed, data = TumGR_Data_Growers,
    model = "within", index = c("patient_id"))

Unbalanced Panel: n=49, T=5-22, N=647

Residuals :
    Min.  1st Qu.   Median  3rd Qu.     Max.
-0.74800 -0.07130  0.00356  0.07100  0.53200

Coefficients :
             Estimate Std. Error t-value  Pr(>|t|)
Time_Elapsed 0.023598   0.001568   15.05 < 2.2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Total Sum of Squares:    14.866
Residual Sum of Squares: 10.777
R-Squared:      0.27505
Adj. R-Squared: 0.25379
F-statistic: 226.501 on 1 and 597 DF, p-value: < 2.22e-16
```

Model Parameters – Ultrasound Diagnostic Categories

ATA Guidelines Table 6	Nodule Characteristics				
Classification	**Solid**	**Hypoechoic**	**Irregular Margins**	**Microcalcifications**	**Taller Than Wide**
High	Y	Y	Y	Y	Y
High	Y	Y	Y	Y	
High	Y	Y	Y		Y
High	Y	Y	Y		
High	Y	Y		Y	Y
High	Y	Y		Y	
High	Y	Y			Y
Intermediate	Y	Y			
?	Y		Y	Y	Y
?	Y		Y	Y	
?	Y		Y		Y
?	Y		Y		
?	Y			Y	Y
?	Y			Y	
?	Y				Y
Low	Y				
Benign		Y	Y	Y	Y
Benign		Y	Y	Y	
Benign		Y	Y		Y
Benign		Y	Y		
Benign		Y		Y	Y
Benign		Y		Y	
Benign		Y			Y
Very Low/Benign					
Benign			Y	Y	Y
Benign			Y	Y	
Benign			Y		Y
Benign			Y		
Benign				Y	Y
Benign				Y	
Benign					Y

Initial Metastases – Pooled Analysis

		Distant Metastases			Lymph Node Metastases		
		Total Patients	Distant Metastases	%	Total Patients	Lymph Node Mets	%
Mantinan	2012	91	1	1.10%	91	4	4.40%
Pelizzo	2006	359	1	0.28%	359	75	20.89%
Caliskan	2012		-		828	218	26.33%
Kim	2015	2372	11	0.46%	2372	932	39.29%
Ardito	2013	149	1	0.67%	149	15	10.07%
Cho	2012		-		205	45	21.95%
Cho	2012		-		322	49	15.22%
Pelizzo	2004		-				
Pedrazzini	2013	231	1	0.43%	231	73	31.60%
Siddiqui	2016		-		86	20	23.26%
Gülben	2008		-		81	10	12.35%
Appetacchia	2002		-				
Haigh	2004	5432	64	1.18%	5432	1396	25.70%
Bilimoria	2007	43917	968	2.20%			
Bilimoria	2007				44732	13307	29.75%
Ito	2003				626	121	19.33%
Adam	2014	61775	584	0.95%	61775	15134	24.50%
Pooled		**114326**	**1631**	**1.43%**	**117289**	**31399**	**26.771%**

Serum TSH – Pooled Analysis

Benign:

		Benign						
Author	**Date**	**Total Patients**	**Mean TSH**	**95% CI Lower**			**95% CI Upper**	**SD TSH**
Jonklaas	2008		1.01	0.84			1.18	0.3469387755
Jin	2010		1.4					
Gerschpacher	2010							
Zafon	2012		1.36					1.62
Fiore	2009	521	0.7		0.3	1.2		0.6671608599
Pooled		**521**	**4.47**					**0.86%**

Malignant:

		Malignant						
Author	**Date**	**Total patients**	**Mean TSH**	**95% CI Lower**	**25pc**	**75pc**	**95% CI Upper**	**SD TSH**
Jonklaas	2008		1.5	1.22			1.78	0.5714285714
Jin	2010		5.5					
Gerschpacher	2010		1.42					0.92
Zafon	2012		2.08					2.1
Fiore	2009	421	1.1		0.7	1.7		0.7412898443
Pooled		**421**	**11.6**					

Postoperative Complications – Pooled Analysis

Surgery Type		Author						
		Date						
					Beta Dist Params			
			Totals Events (numerator)	*Total Population Included (denominator)*	*Alpha*	*Beta*	*Event Probability*	*Event SE sqrt(p(1-p)/n)*
Lobectomy	**Duratio**	**Lobectomy Patients**						
	Short	Airway Problem	5	903	5	898	0.55%	0.25%
	Long	Hypocalcemia	30	1441	30	1411	2.08%	0.38%
	Short	Wound Infection	2	903	2	901	0.22%	0.16%
	Short	Transient Hypoparathyroidism	475	21813	475	21338	2.18%	0.10%
	Long	Permanent Hypoparathyroidism	1	1910	1	1909	0.05%	0.05%
	Short	Temporary Vocal Cord Paralysis	50	3311	50	3261	1.51%	0.21%
	Long	Permanent Vocal Cord Paralysis	11	1653	11	1642	0.67%	0.20%
	N/A	RLN Injury	114	20139	114	20025	0.57%	0.05%
	Short	Bleeding	9	2072	9	2063	0.43%	0.14%
	Short	Seroma	0	414	0	414	0.00%	0.00%
	Short	Chyle Leak	0	414	0	414	0.00%	0.00%
	Short	Tracheal Leak	0	414	0	414	0.00%	0.00%
	Long	Death Within 30 days	3	1317	3	1314	0.23%	0.13%
Total Thyroidectomy		**Total Thyroidectomy Patients**						
	Short	Airway Problem	40	4451	40	4411	0.90%	0.14%
	Long	Hypocalcemia	721	5418	721	4697	13.31%	0.46%
	Short	Wound Infection	9	4451	9	4442	0.20%	0.07%
	Short	Transient Hypoparathyroidism	3079	34620	3079	31541	8.89%	0.15%
	Long	Permanent Hypoparathyroidism	39	2758	39	2719	1.41%	0.22%
	Short	Temporary Vocal Cord Paralysis	599	40265	599	39666	1.49%	0.06%
	Long	Permanent Vocal Cord Paralysis	14	2159	14	2145	0.65%	0.17%
	N/A	RLN Injury	0	428	0	428	0.00%	0.00%
	Short	Bleeding	49	6827	49	6778	0.72%	0.10%
	Short	Seroma	0	428	0	428	0.00%	0.00%
	Short	Chyle Leak	3	583	3	580	0.51%	0.30%
	Short	Tracheal Leak	0	428	0	428	0.00%	0.00%
	Long	Death Within 30 days	11	5488	11	5477	0.20%	0.06%
Combined		**Total Patients**						
	Short	Airway Problem	45	5354	45	5309	0.84%	0.12%
	Long	Hypocalcemia	729	6529	729	5800	11.17%	0.39%
	Short	Wound Infection	27	6374	27	6347	0.42%	0.08%
	Short	Transient Hypoparathyroidism	76	842	76	766	9.03%	0.99%
	Long	Permanent Hypoparathyroidism	11	842	11	831	1.31%	0.39%
	Short	Temporary Vocal Cord Paralysis	18	1175	18	1157	1.53%	0.36%
	Long	Permanent Vocal Cord Paralysis	14	1175	14	1161	1.19%	0.32%
	N/A	RLN Injury	32	8029	32	7997	0.40%	0.07%
	Short	Bleeding	50	7371	50	7321	0.68%	0.10%
	Short	Seroma	38	1862	38	1824	2.04%	0.33%
	Short	Chyle Leak	5	2017	5	2012	0.25%	0.11%
	Short	Tracheal Leak	0	842	0	842	0.00%	0.00%
	Long	Death Within 30 days	13	5354	13	5341	0.24%	0.07%

Surgery Type		Author	Caliskan	Bhattacharyya	*Barczynski	*Giles	*Pappalardo	*Yang	Hundahl	DeGroot	Roh	Dralle	Erbil	Filho	Bergamaschi	Vashishta	Kwon
		Date	2012	2002	2010	2004	1998	2009	2000	1990	2007	2004	2006	2005	1998	2012	2017
			Table 2	Results Section	m Cirocchi Revi	m Cirocchi Revi	m Cirocchi Revi	m Cirocchi Revi	Table 9	Abstract	Table 3	Table 2 & Text	Table 1	Table 2	Table 3	Table 2	Table 4
Lobectomy	Duratio	Lobectomy Patients	414		379	109	72	181	903	178				538	374	19725	755
	Short	Airway Problem							5								
	Long	Hypocalcemia							30					0			
	Short	Wound Infection							2								
	Short	Transient Hypoparathyroidism	8		12	1	13	9		15						417	0
	Long	Permanent Hypoparathyroidism	0		0	0	1	0									0
	Short	Temporary Vocal Cord Paralysis			24	1	2	3	8					2	10		2
	Long	Permanent Vocal Cord Paralysis			5	0	1	0						2	3		
	N/A	RLN Injury	-													114	
	Short	Bleeding	-						9								7
	Short	Seroma	-														
	Short	Chyle Leak	-														
	Short	Tracheal Leak	-														
	Long	Death Within 30 days	-						3								
Total Thyroidectomy		Total Thyroidectomy Patients	428	517	191	109	69	165	4451		155		520	295	655	31862	1276
	Short	Airway Problem							40								
	Long	Hypocalcemia		32					503		36			150			
	Short	Wound Infection							9								
	Short	Transient Hypoparathyroidism	68		21	2	24	11					45			2738	170
	Long	Permanent Hypoparathyroidism	11		1	0	2	0					2				23
	Short	Temporary Vocal Cord Paralysis		6	21	1	2	3	64		9		10	9	45	417	12
	Long	Permanent Vocal Cord Paralysis			4	0	0	0			5		2	1	2		
	N/A	RLN Injury	-														
	Short	Bleeding	-	5					30		1						13
	Short	Seroma	-														
	Short	Chyle Leak	-								3						
	Short	Tracheal Leak	-														
	Long	Death Within 30 days		1					10				0				
Combined		Total Patients	842						5354		155	1833		1020			
	Short	Airway Problem							45								
	Long	Hypocalcemia							533		36			160			
	Short	Wound Infection							11					16			
	Short	Transient Hypoparathyroidism	76														
	Long	Permanent Hypoparathyroidism	11														
	Short	Temporary Vocal Cord Paralysis									9			9			
	Long	Permanent Vocal Cord Paralysis									5			9			
	N/A	RLN Injury	4						0			28					
	Short	Bleeding	1						39		1			9			
	Short	Seroma	0											38			
	Short	Chyle Leak	0								3			2			
	Short	Tracheal Leak	0														
	Long	Death Within 30 days							13								

Recurrence Rates – Pooled Analysis

			Total Thyroidectomy							Lobectomy						
Author	Year		Total (n)	Recurrence (n)	Followup (yrs)	Recurrence	Annualized Probability	Weighted Annualized Probability		Total (n)	recurrence (n)	Followup (yrs)	Recurrence	Annualized Probability	Weighted Annualized Probability	
Cho	2015		182	8	5.9	4.40%	0.76%	0.003%	0.37%	154	8	4.5	5.20%	1.18%	0.015%	
Lee	2014		1245	26	10	2.09%	0.21%	0.005%	2.51%	773	15	10	6.50%	0.67%	0.042%	
Mantinan	2012		77	7	12.9	9.09%	0.74%	0.001%	0.16%	14	1	12.9	7.10%	0.57%	0.001%	
Pelizzo	2006		359	1	8.5	0.28%	0.03%	0.000%	0.72%	44	5	8.5	11.36%	1.41%	0.005%	
Kuo	2011		52	6	8.1	11.54%	1.50%	0.002%	0.10%	9	0	8.1	0.00%	0.00%	0.000%	
Caliskan	2012		428	7	5.42	1.64%	0.30%	0.003%	0.86%	414	12	5.42	2.90%	0.54%	0.018%	
Kim	2015		1140	27	5.6	2.37%	0.43%	0.010%	2.30%	521	9	5.6	1.73%	0.31%	0.013%	
Kim	2015		631	41	5.6	6.50%	1.19%	0.015%	1.27%	17	1	5.6	5.88%	1.08%	0.001%	
Ardito	2012		135	28	5.4	20.74%	4.21%	0.011%	0.27%	14	0	5.4	0.00%	0.00%	0.000%	
Jin-Kyu Cho	2012		294	9	4.02	3.06%	0.77%	0.005%	0.59%	233	8	4.02	3.43%	0.87%	0.016%	
Pelizzo	2004		126	0	6.5	0.00%	0.00%	0.000%	0.25%	23	3	6.5	13.04%	2.13%	0.004%	
Pedrazzini	2013		177	10	12	5.65%	0.48%	0.002%	0.36%	54	5	12	9.26%	0.81%	0.004%	
Siddiqui	2016		148	5	3.5	3.38%	0.98%	0.003%	0.30%	36	0	3.5	0.00%	0.00%	0.000%	
Gülben	2008		64	1	6.92	1.56%	0.23%	0.000%	0.13%	17	0	6.92	0.00%	0.00%	0.000%	
Appetacchia	2002		106	2	10	1.89%	0.19%	0.000%	0.21%	14	0	10	0.00%	0.00%	0.000%	
Bilimoria	2007		43227	3328	10	7.70%	0.80%	0.695%	87.14%	8946	877	10	9.80%	1.03%	0.744%	
Kwon	2017		688	11	8.5	1.60%	0.19%	0.003%	1.39%	688	26	8.5	3.78%	0.45%	0.025%	
			528	10	10	1.89%	0.19%	0.002%	1.06%	361	0	10	0.00%	0.00%	0.000%	
			49607	3527			**Pooled Estimate Annual**	**0.760%**	**0.96%**	**12332**	**970**			**Pooled Estimate Annual**	**0.889%**	
							Crude Estimate Annual	**0.734%**						**Crude Estimate Annual**	**0.613%**	

Analytic Code

PTMC_Linear_Model 5.R

```
# Load Packages
# library(plm)
# library(gplots)
library(car)
library(plyr)
# library(ggplot2)
library(tumgr)
library(stats)
library(lmtest)
# library(ggfortify)
library(MASS)


# Data file was modified within SQL Server to drop any rows where the dates
# were the same but the tumor size was different. I decided to keep the
# largest tumor size value of the duplicates.
# Read in Data and select the patients we want to keep
PTMC <- read.csv('/Users/craigwhite3/Google Drive/Grad School/Harvard/Research/Papillary Thyroid
Cancer/Background/Natural History Data/PTMC Data TXT File - Clean - Unique.csv')
#Get a list of patients who are under age 18 and drop them
bad.patients.age <- as.numeric(unique(PTMC$patient_id[(PTMC$Age <18)]))
PTMC <- PTMC[!(PTMC$patient_id %in% bad.patients.age),]
# Get a list of patients who have tumor size measurements of 0 and drop them
bad.patients.tumor_size <- as.numeric(unique(PTMC$patient_id[(PTMC$Tumor_Size < 4)]))
PTMC <- PTMC[!(PTMC$patient_id %in% bad.patients.tumor_size),]

# Create the master data table with only patients who have more than 3 readings
bad.patients.readings <- as.numeric(names(table(PTMC$patient_id)))[table(PTMC$patient_id)<3]
Thyroid_Master<-PTMC[!PTMC$patient_id %in% bad.patients.readings,]

TumGR_Data <- Thyroid_Master[,c("patient_id", "Time_Elapsed", "Tumor_Size")]
TumGR_Data <- rename(TumGR_Data, c("patient_id"="name", "Time_Elapsed"="date",
"Tumor_Size"="size"))

###### Take a look at the data. Include this code if you want
###### to view some of the data visually and for checking
# head(Thyroid_Master)
# scatterplot(Tumor_Size~Time_Elapsed|patient_id, boxplots=FALSE, smooth=FALSE,
data=Thyroid_Master, legend.columns = 19)
# plotmeans(Tumor_Size ~ patient_id, main="Heterogeneity across patients", data=Thyroid_Master)
# hist(Thyroid_Master$Tumor_Size, prob=TRUE)
# curve(dnorm(x, mean=mean(Thyroid_Master$Tumor_Size), sd=sd(Thyroid_Master$Tumor_Size)),
col="darkblue", lwd=2, add=TRUE, yaxt="n")
# shapiro.test(Thyroid_Master$Tumor_Size)
# Look at the density of the time distribution. This is obviously not normal, looks almost
bimodal...
# plot(density(Thyroid_Master$Time_Elapsed))

##############################################################################################
######
#----------------------------------Tumor Growth Models (exponential)---------------------------
-----#
#-----------------------------------------------------------------------------------------------
-----#
# Tumor Growth Model Fits - Does not utilize any covariates.
# Automagically identifiies growers and shrinkers.
# Need to use days in time field since it requires integer readings (I think). Doesn't work with
years
#-----------------------------------------------------------------------------------------------
-----#
#-----------------------------------------------------------------------------------------------
-----#
model.fit <- gdrate(TumGR_Data, pval = 0.05, plots = FALSE)
model.gx <- model.fit$results[model.fit$results$selectedFit == "gx",]
model.dx <- model.fit$results[model.fit$results$selectedFit == "dx",]
model.not_fit <- model.fit$results[model.fit$results$selectedFit == "not fit",]
```

```
# Get the three groups of patients based upon growth status
Thyroid_Master$Time_Elapsed <- Thyroid_Master$Time_Elapsed/365 # Convert days to years
TumGR_Data_Growers <- Thyroid_Master[Thyroid_Master$patient_id %in% model.gx$name,]
TumGR_Data_Shrinkers <- Thyroid_Master[Thyroid_Master$patient_id %in% model.dx$name,]
TumGR_Data_Stable <- Thyroid_Master[Thyroid_Master$patient_id %in% model.not_fit$name,]

#----------------------------------Linear Models for Stable---------------------------------
-#
#-------------------------------------------------------------------------------------------
-----#
# Using the fitted models from the exponential models just run, create linear models for the
group of
# patients for whom the exponential models didn't fit either growth of decay (Assume too flat for
fit)
# plot(Model.fe.Stable, las = 1, which = c(1:6))
# qqPlot(Model.fe.Stable)
#-------------------------------------------------------------------------------------------
-----#
#-------------------------------------------------------------------------------------------
-----#
# Create the patient level fixed effects linear model(s) using only the non-growing patients
# Option 1
Model.fe.Stable <-lm(Tumor_Size ~ Time_Elapsed + Age + factor(patient_id),
data=TumGR_Data_Stable)
# summary(Model.fe.Stable) # summary of model
# autoplot(Model.fe.Stable) # Diagnostics look OK, QQ plot is good, and residuals appear
homoscedastic. Pattern due to integer nature of data?
# Look at the residuals and see if they are normally distributed, if not, we should double check
model spec and / or run with robust errors
# plot(density(Model.fe.Stable$residuals)) # Do these look normal? SW test says no.
# curve(dnorm(x, mean=mean(Model.fe.Stable$residuals), sd=sd(Model.fe.Stable$residuals)),
col="darkblue", lwd=2, add=TRUE, yaxt="n")
# coeftest(Model.fe.Stable, vcov = vcovHC(Model.fe.Stable, "HC1")) # Robust SEs make very little
difference to estimates.
# shapiro.test(Model.fe.Stable$residuals) # SW rejects the null, but this may be due to
integerization again!

# Generate Fitted Values and plot model fits.
# yhatGR_Stable <- Model.fe.Stable$fitted
# TumGR_Data_Stable["yhatGR_Stable"] <- yhatGR_Stable
# scatterplot(yhatGR_Stable~TumGR_Data_Stable$Time_Elapsed|TumGR_Data_Stable$patient_id,
boxplots=FALSE, xlab="Time_Elapsed", ylab="TumGR_Data_Stable",smooth=FALSE, legend.columns = 17)
# model.fit.line <- abline(lm(TumGR_Data_Stable$Tumor_Size~TumGR_Data_Stable$Time_Elapsed +
factor(TumGR_Data_Stable$patient_id)),lwd=3, col="red")
# plot <- ggplot(TumGR_Data_Stable, aes(x = Time_Elapsed, y = Tumor_Size, color =
factor(patient_id))) + geom_point() + geom_smooth(method = lm, se=FALSE)
# plot + theme(legend.position="none")

Stable_Growth_Rate_Per_Year <- coef(summary(Model.fe.Stable))["Time_Elapsed", c("Estimate", "Std.
Error")]
# Stable_Growth_Rate_Per_Year <- Model.fe.Stable$coefficients["Time_Elapsed"]
# Stable_SD_Growth_Rate_Per_Year <- sqrt(diag(vcov(Model.fe.Stable)))["Time_Elapsed"]

#############################################################################################
######

#----------------------------------Linear Models for Growers--------------------------------
-----#
#-------------------------------------------------------------------------------------------
-----#
# Using the fitted models from the exponential models just run, create linear models for the
group of
# patients for whom the exponential models fit a growth model
#-------------------------------------------------------------------------------------------
-----#
#-------------------------------------------------------------------------------------------
-----#
# Create the patient level fixed effects linear model(s) using only the patient with growing
tumors
# OPTION 1 - Log the DV, which we think is exponential, so that we linearize it.
Model.fe.Growers <-lm(log(Tumor_Size) ~ Time_Elapsed + Age + factor(patient_id),
data=TumGR_Data_Growers)
```

```
# summary(Model.fe.Growers) # summary of model (don't forget to exponentiate the coefficients!)
# autoplot(Model.fe.Growers) # Diagnostics look OK, QQ plot is good, and residuals appear
homoscedastic conditional on interegerization. Pattern due to integer nature of data?
# Look at the residuals and see if they are normally distributed
# If not, we should doule check model spec and / or run with robust errors
# plot(density(Model.fe.Growers$residuals)) # Do these look normal?
# curve(dnorm(x, mean=mean(Model.fe.Growers$residuals), sd=sd(Model.fe.Growers$residuals)),
col="darkblue", lwd=2, add=TRUE, yaxt="n")
# coeftest(Model.fe.Growers, vcov = vcovHC(Model.fe.Growers, "HC1")) # Robust SEs make very
little difference to estimates.
# shapiro.test(Model.fe.Growers$residuals) # bummer SW rejects the null
# bptest(log(Tumor_Size) ~ Time_Elapsed + factor(patient_id), data=TumGR_Data_Growers,
studentize=TRUE) # bummer... BP rejects the null, but I think this is because of the integer
values issue.


#---------------------------------- GENERATE SOME PREDICTIONS ----------------------------------
-----#
# newdata <- data.frame(Time_Elapsed = c(0,10), patient_id = 101, Age = 65, Female  = 1, RadHx =
0, FamHxPTC = 0, Susp_LNM = 0, Susp_MF = 0)
# prediction <- predict(Model.fe.Growers, newdata = newdata, se.fit = TRUE)
# prediction$fit <- exp(prediction$fit) #convert log values to mm size
# prediction

Growers_Growth_Rate_Per_Year <- coef(summary(Model.fe.Growers))["Time_Elapsed", c("Estimate",
"Std. Error")]
# Confint.Growers <- confint(Model.fe.Growers, parm = "Time_Elapsed", level = 0.95)
# Growers_SD_Growth_Rate_Per_Year <- (Confint.Growers[2] - Confint.Growers[1])/3.92 *
sqrt(length(unique(TumGR_Data_Growers$patient_id)))
# Alternative method # Growers_SD_Growth_Rate_Per_Cycle <-
sqrt(diag(vcovHC(Model.fe.Growers)))["Time_Elapsed"]
##########################################################################################
######
# OPTION 2 - NLS model using exp covariate for Time_Elapsed
# library(nlstools)
# Model.fe.Growers.nls <-nls(Tumor_Size ~ Const + exp(Time_Coef*Time_Elapsed),
data=TumGR_Data_Growers, start = list(Const=0, Time_Coef=0))
# summary(Model.fe.Growers.nls) # summary of model (don't forget to exponentiate the
coefficients!)
# Resids <- nlsResiduals(Model.fe.Growers.nls) # Diagnostics look OK, QQ plot is good, and
residuals appear homoscedastic conditional on interegerization. Pattern due to integer nature of
data?
# plot(Resids, which = 0)

#---------------------------------- GENERATE SOME PREDICTIONS For Model Option 2----------------
-----#
# newdata <- data.frame(Time_Elapsed = c(0,10), patient_id = 101, Age = 65, Female  = 1, RadHx =
0, FamHxPTC = 0, Susp_LNM = 0, Susp_MF = 0)
# prediction <- predict(Model.fe.Growers.nls, newdata = newdata, se.fit = TRUE)
# prediction$fit <- exp(prediction$fit) #convert log values to mm size
# prediction

#----------------------------------Linear Models for Shrinkers---------------------------------
-----#
#---------------------------------------------------------------------------------------------
-----#
# Using the fitted models from the exponential models just run, create linear models for the
group of
# patients for whom the exponential models fit a growth model
#---------------------------------------------------------------------------------------------
-----#
#---------------------------------------------------------------------------------------------
-----#
# Create the patient level fixed effects linear model(s) using only the patient with growing
tumors
# Option 1 - Log the DV, which we think is exponential, so that we linearize it.
Model.fe.Shrinkers <-glm(log(Tumor_Size) ~ Time_Elapsed + Age + factor(patient_id),
data=TumGR_Data_Shrinkers)
# summary(Model.fe.Shrinkers) # summary of model (don't forget to exponentiate the coefficients!)
# autoplot(Model.fe.Shrinkers) # Diagnostics look OK, QQ plot is good, and residuals appear
homoscedastic conditional on interegerization. Pattern due to integer nature of data?
# Look at the residuals and see if they are normally distributed
# If not, we should doule check model spec and / or run with robust errors
```

```
# plot(density(Model.fe.Shrinkers$residuals)) # Do these look normal?
# curve(dnorm(x, mean=mean(Model.fe.Shrinkers$residuals), sd=sd(Model.fe.Shrinkers$residuals)),
col="darkblue", lwd=2, add=TRUE, yaxt="n")
# coeftest(Model.fe.Shrinkers, vcov = vcovHC(Model.fe.Shrinkers, "HC1")) # Robust SEs make very
little difference to estimates.
# shapiro.test(Model.fe.Shrinkers$residuals) # bummer SW rejects the null
# bptest(log(Tumor_Size) ~ Time_Elapsed + factor(patient_id), data=TumGR_Data_Shrinkers,
studentize=TRUE) # bummer... BP rejects the null, but I think this is because of the integer
values issue.

Shrinkers_Growth_Rate_Per_Year <- coef(summary(Model.fe.Shrinkers))["Time_Elapsed", c("Estimate",
"Std. Error")]
# Shrinkers_Growth_Rate_Per_Year <- Model.fe.Shrinkers$coefficients["Time_Elapsed"]
# Shrinker_SD_Growth_Rate_Per_Year <- coef(summary(Model.fe.Shrinkers))["Time_Elapsed", "Std.
Error"]
# Confint.Shrinkers <- confint(Model.fe.Shrinkers, parm = "Time_Elapsed", level = 0.95)
# Shrinker_SD_Growth_Rate_Per_Year <- (exp(Confint.Shrinkers[2]) -
exp(Confint.Shrinkers[1]))/3.92 * sqrt(length(unique(TumGR_Data_Shrinkers$patient_id)))

# Shrinker_SD_Growth_Rate_Per_Year <- sqrt(diag(vcov(Model.fe.Shrinkers)))["Time_Elapsed"]
#-------------------------------FOR TESTING AND VALIDATION ONLY---------------------------------
-----#
#-------------------------------Panel Linear Model-----------------------------------------------
-----#
#-------------------------------------------------------------------------------------------------
-----#
# Use PLM package for panel linear model. Pooling works which implies the data are in the right
format.
# Estimates on Within model are same as with alternate FE model specification! Good.
# p-val is the same also
#
#-------------------------------------------------------------------------------------------------
-----#
#-------------------------------------------------------------------------------------------------
-----#
# Thyroid.plm.fe <- plm(log(Tumor_Size) ~ Time_Elapsed, data=TumGR_Data_Growers, index =
c("patient_id"), model="within")
# summary(Thyroid.plm.fe)
# summary(fixef(Thyroid.plm.fe))
# bptest(Tumor_Size~Age + Time_Elapsed + Female, data=TumGR_Data_Growers, studentize = TRUE)
# coeftest(Thyroid.plm.fe, vcovHC)

#-------------------------------Regression Mdoel Type Selection----------------------------------
-----#
#-------------------------------------------------------------------------------------------------
-----#
# Do we need to use a discrete linear DV regression? If so, I have no idea which one...
# Since this is panel data, and the DV takes integer values (technically they should be real
# valued but they're being rounded to integer values for the tumor size in almost all cases)
# What should we do? Poisson and NegBin don't really apply, since these are for count data from
# distinct individuals or samples. This isn't that type of data.
# I think it's safe to assume that the DV is actually a real valued variable for a couple of
reasons
# 1) Some of the values are real values, so if we made them integers we'd have to decide what to
do
# with the,. Also, there's nothing technically wrong with treating integers as real values,
especially
# if we know they were drawn from a real valued dataset. What we're really saying is that the DV
has
# some measurement error, and that the error is probably unbiased, so it's OK.
# 2) If we remain cognizant of this, we can interpret the BP and SW tests accordingly. It
basically
# invalidates the BP test for homoscedasticity. Since the residuals exhibit a pattern that is
# not symmetrical around each integer value, we'll never get a good BP test result, I expect.
# Model.NegBin <- glm.nb(Tumor_Size ~ Time_Elapsed + Age + factor(patient_id),
data=TumGR_Data_Growers)
# summary(Model.NegBin)
rm(model.dx)
rm(model.gx)
rm(model.not_fit)
rm(TumGR_Data)
rm(Thyroid_Master)
rm(bad.patients.readings)
```

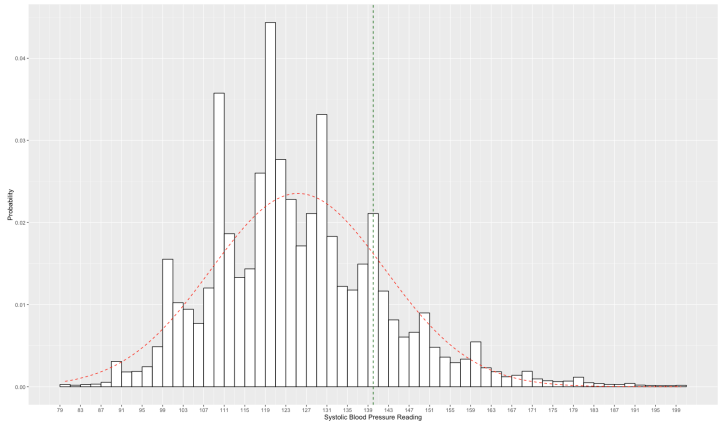
```
rm(bad.patients.age)
rm(bad.patients.tumor_size)
rm(Model.fe.Shrinkers)
rm(Model.fe.Growers)
rm(Model.fe.Stable)
rm(model.fit)
```

Appendix 3 – Supplementary Materials for Chapter 3

Initial Analyses

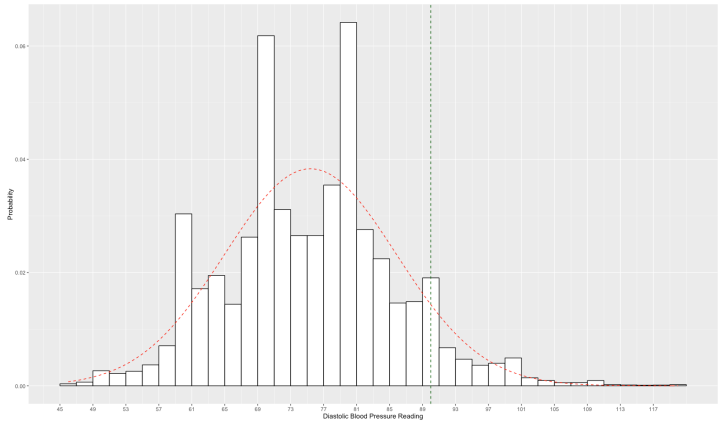
DISTRIBUTION OF SBP READINGS

- Distribution of Systolic BP scores is "peaky" with peaks at multiples of 10's



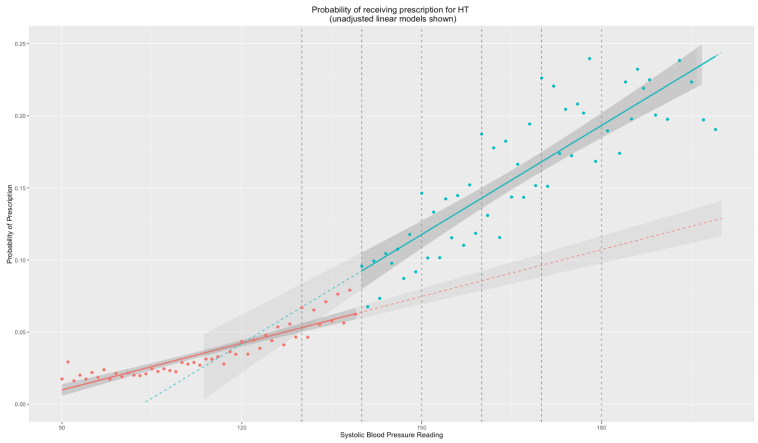
DISTRIBUTION OF DBP READINGS

- Distribution of Diastolic BP scores is "peaky" with peaks at multiples of 10's



SBP PROBABILITY OF RECEIVING HT PRESCRIPTION

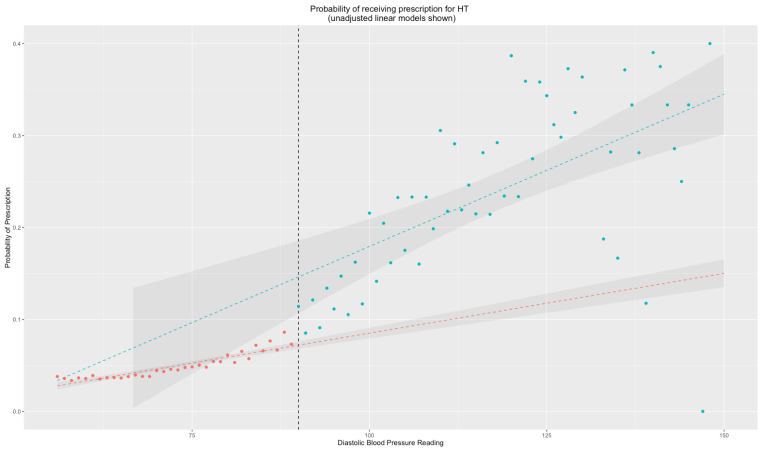
- For SBP, the probability of receiving a prescription for an antihypertensive is affected by SBP score (higher score -> higher probability) and unexpectedly, by evenness of the score. (even reading -> Higher probability)



red = below 140mmHg guideline threshold, blue = at or above 140mmHg threshold

DBP PROBABILITY OF RECEIVING HT PRESCRIPTION

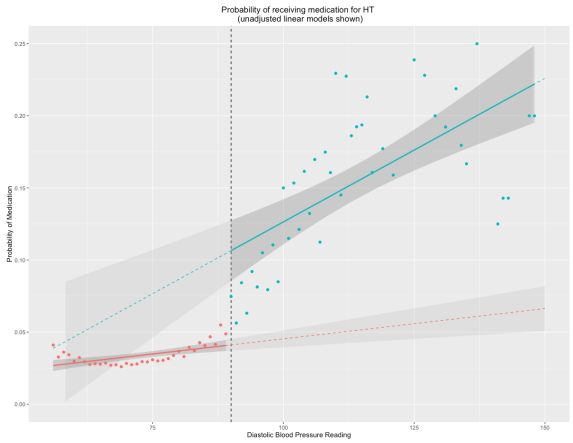
- For DBP, the probability of receiving a prescription for an antihypertensive is affected by DBP score (higher score -> higher probability) and unexpectedly, by evenness of the score. (even reading -> Higher probability)



red = below 90mmHg guideline threshold, blue = at or above 90mmHg threshold

DBP PROBABILITY OF BEING ON HT MEDICATION

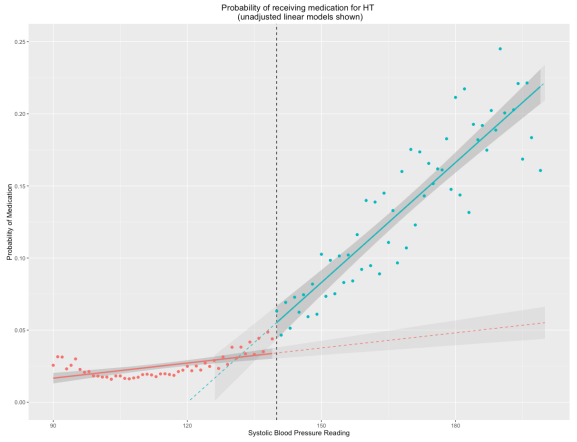
Diastolic Chart



red = below 90mmHg guideline threshold,
blue = at or above 90mmHg threshold

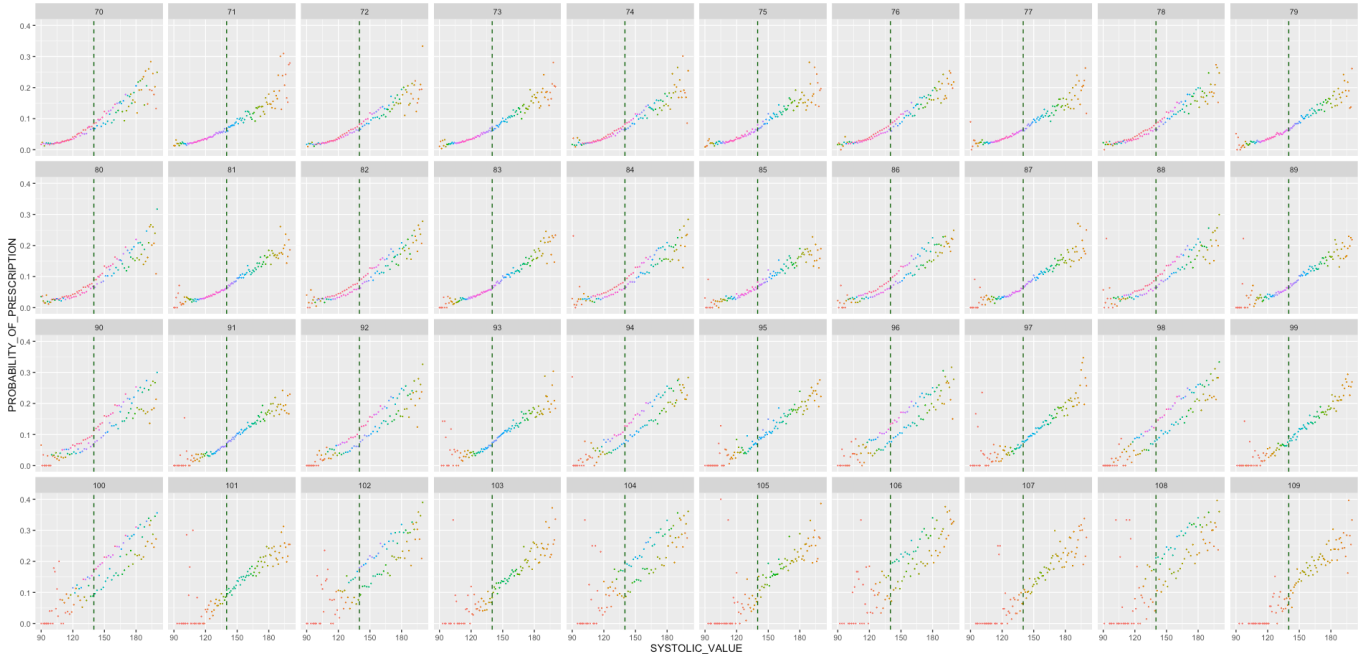
- For DBP and SBP, the probability of being on Medication for an antihypertensive is affected by BP (higher -> higher probability) and unexpectedly, by evenness of the score. (even reading -> Higher probability)

Systolic Chart



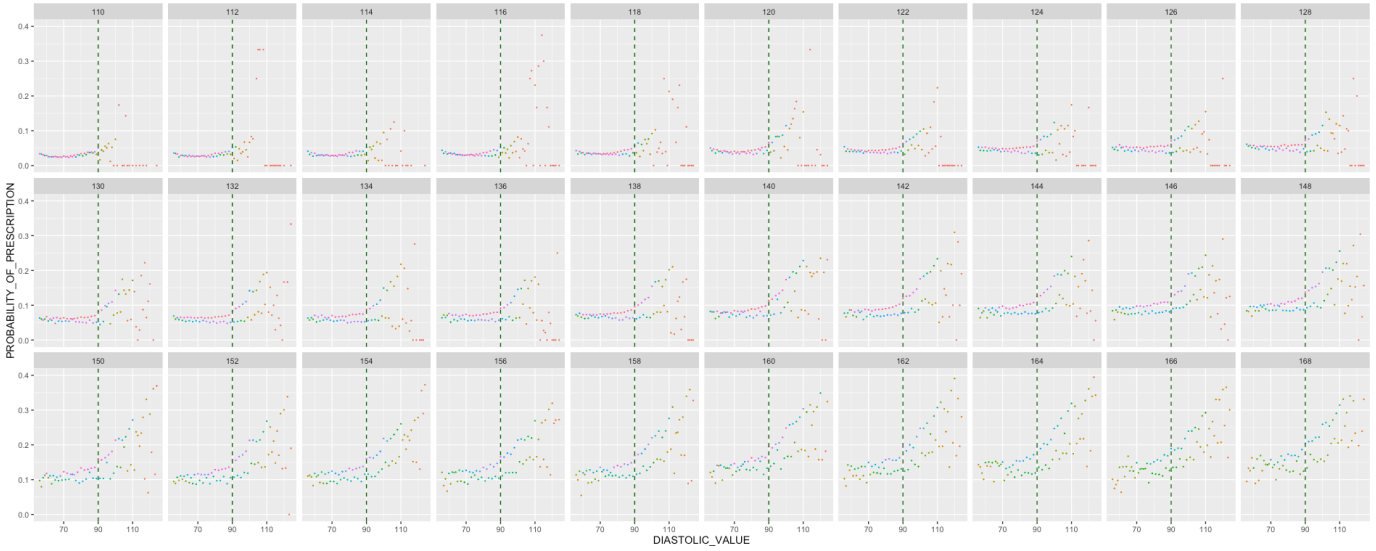
red = below 140mmHg guideline threshold,
blue = at or above 140mmHg threshold

ODD-EVEN PHENOMENON EXISTS THROUGHOUT THE DATA



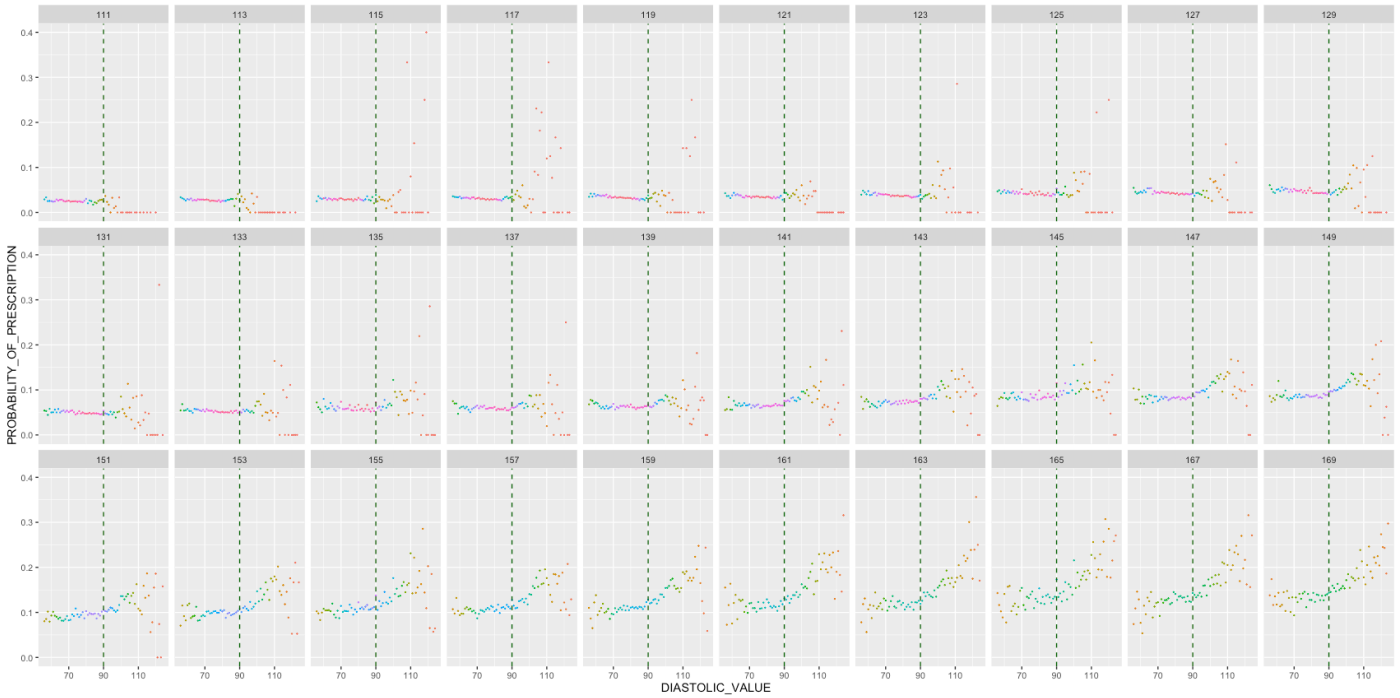
Each sub-chart is for a specific DBP showing all values of SBP and probability to receive a prescription. It can be observed that for each even numbered DBP, there is a noticeable separation in the probability of receiving a prescription for almost all even values of SBP, and that this disparity seems to increase as diastolic BP increases (e.g. 82, 84, 86 show less disparity than 102, 104, 106)

EVEN-NUMBERED SBP READINGS ONLY



The following shows the probability of receiving medication for any DBP, given a specific SBP. Each chart represents a specific SBP, and all DBP readings for that SBP.

ODD-NUMBERED SBP READINGS ONLY



The following shows the probability of receiving medication for any DBP, given a specific SBP. Each chart represents a specific SBP, and all DBP readings for that SBP. Compare this to the slide preceding.

Analytic Code

Hypertension Functions

```
################################################################################
################## Formula to generate the predictions ##########################
# Variables:
# model_object = glm model object created by speedglm or glm
#
# returns: a data.frame with the predictions for each systolic BP value
#
################################################################################
generate_predictions <- function(model_object, age_is_factor = FALSE, age = 18, systolic_values =
data.frame(seq(101,200,1)), physician = 1, gender = 0, race = 0, ethnicity = 0, marital = 0,
employment = 1, comorbid = 0 )
{
  # TODO: check for model object validity here. e.g. Make sure it is an lm or glm object
  glm.fit.systolic <- data.frame(as.numeric(systolic_values))
  colnames(prediction_data)[1] = "SYSTOLIC_VALUE"
  prediction_data$EVEN_SYSTOLIC <- 1-prediction_data$SYSTOLIC_VALUE %% 2
  prediction_data$SHOULD_BE_TREATED <- prediction_data$SYSTOLIC_VALUE > 139

  prediction_data$SYSTOLIC_VALUE_5MM <- cut(prediction_data$SYSTOLIC_VALUE, breaks =
seq(min(systolic_values), max(systolic_values), 5), labels = c("SBP 101-105", "SBP 106-110", "SBP
111-115", "SBP 116-120", "SBP 121-125", "SBP 126-130", "SBP 131-135", "SBP 136-140", "SBP 141-
145", "SBP 146-150", "SBP 151-155", "SBP 156-160", "SBP 161-165", "SBP 166-170", "SBP 171-175",
"SBP 176-180", "SBP 181-185", "SBP 186-190", "SBP 191-195", "SBP 196-200"), ordered_result =
FALSE)
  #prediction_data$DIASTOLIC_VALUE_5MM <- cut(prediction_data$DIASTOLIC_VALUE, breaks = seq(55,
125, 5), labels = c("DBP 56-60", "DBP 61-65", "DBP 66-70", "DBP 71-75", "DBP 76-80", "DBP 81-85",
"DBP 86-90", "DBP 91-95", "DBP 96-100", "DBP 101-105", "BP 106-110", "BP 111-115", "BP 116-120",
"BP 121-125"), ordered_result = FALSE)

  prediction_data$IS_PHYSICIAN_CODE <- factor(physician, levels = c(0,1), labels = c("Non-
Physician", "Physician"))
  prediction_data$PATIENT_GENDER_CODE <- factor(gender, levels = c("0", "1"), labels = c("Male",
"Female"))
  prediction_data$PATIENT_RACE_CODE <- factor(race, levels = c("0", "1", "2", "3", "4", "9",
"99"), labels = c("White", "Black","Asian","Native-American","Hawaii/Pac. Island", "Unknown",
"Not-Entered"))
  prediction_data$PATIENT_ETHNICITY_CODE <- factor(ethnicity, levels = c("0", "1", "9", "99"),
labels = c("Non-Hispanic", "Hispanic", "Unknown", "Not Entered"))
  prediction_data$PATIENT_MARITAL_STATUS_CODE <- factor(marital, levels = c("0", "1", "2", "3",
"4", "5", "9", "99"), labels = c("Married", "Single", "Widowed/Widower", "Divorced", "Separated",
"Partnered", "Unknown", "Not-Entered"))
  prediction_data$PATIENT_EMPLOYMENT_STATUS_CODE <- factor(employment, levels = c("0", "1", "2",
"9", "99"), labels = c("Unemployed", "Employed", "Retired", "Unknown", "Not-Entered"))
  prediction_data$EVEN_SYSTOLIC <- factor(prediction_data$EVEN_SYSTOLIC, levels = c(0,1), labels
= c("Odd", "Even"))
  prediction_data$SHOULD_BE_TREATED <- factor(prediction_data$SHOULD_BE_TREATED, levels =
c("FALSE","TRUE"), labels = c("No", "Yes"))
  prediction_data$HasComorbidities <- factor(comorbid, levels = c(0,1), labels = c("FALSE",
"TRUE"))
  if(age_is_factor) {prediction_data$AGE_ON_OBS_DATE <- cut(age, breaks = c(17, 30, 40, 50, 60,
70, 80, Inf), labels = c("Age 18-30", "Age 30-40", "Age 40-50", "Age 50-60", "Age 60-70", "Age
70-80", "Age 80+"))}
  if(!age_is_factor) {prediction_data$AGE_ON_OBS_DATE <- age}
  prediction_data$predicted <- exp(predict(model_object, newdata = prediction_data))
  return(prediction_data)
}

################################################################################
################## Formula to run the regressions ###############################
# Variables:
# reg_eqn = equation with regression formula
# dataset = dataset with data for the regression. data.frame
# regression_name = friendly name for the regression, used for excel worksheet name
```

```
#
#################################################################################
run_logistic_regression <- function(reg_eqn, dataset, regression_name)
{
  glm.fit <- speedglm(formula = reg_eqn, data = dataset, family = binomial(link = "logit"),
na.action = na.exclude, fitted = TRUE)
  results <- na.omit(as.data.frame(coef(summary(glm.fit))))
  results$Estimate <- na.omit(exp(coef(glm.fit)))
  colnames(results)[1] = c("Odds_Ratio")
  results$Probability <- results[, "Odds_Ratio"]/(1 + results[, "Odds_Ratio"])
  #results$95CI_Lower <- confint.default(glm.fit)$
  Today <- format(Sys.time(), format="%B %d %Y")
  xls_filename <- paste0('Hypertension Regression Outputs Auto Generated Sample ',Today,'.xlsx',
sep="")
  write.xlsx(results, xls_filename, paste(regression_name, ' n=', nrow(dataset), sep = ""),
append = TRUE)
  return(glm.fit)
}

# Multiple plot function
#
# ggplot objects can be passed in ..., or to plotlist (as a list of ggplot objects)
# - cols:   Number of columns in layout
# - layout: A matrix specifying the layout. If present, 'cols' is ignored.
#
# If the layout is something like matrix(c(1,2,3,3), nrow=2, byrow=TRUE),
# then plot 1 will go in the upper left, 2 will go in the upper right, and
# 3 will go all the way across the bottom.
#
multiplot <- function(..., plotlist=NULL, file, cols=1, layout=NULL) {
  library(grid)

  # Make a list from the ... arguments and plotlist
  plots <- c(list(...), plotlist)

  numPlots = length(plots)

  # If layout is NULL, then use 'cols' to determine layout
  if (is.null(layout)) {
    # Make the panel
    # ncol: Number of columns of plots
    # nrow: Number of rows needed, calculated from # of cols
    layout <- matrix(seq(1, cols * ceiling(numPlots/cols)),
                     ncol = cols, nrow = ceiling(numPlots/cols))
  }

  if (numPlots==1) {
    print(plots[[1]])

  } else {
    # Set up the page
    grid.newpage()
    pushViewport(viewport(layout = grid.layout(nrow(layout), ncol(layout))))

    # Make each plot, in the correct location
    for (i in 1:numPlots) {
      # Get the i,j matrix positions of the regions that contain this subplot
      matchidx <- as.data.frame(which(layout == i, arr.ind = TRUE))

      print(plots[[i]], vp = viewport(layout.pos.row = matchidx$row,
                                      layout.pos.col = matchidx$col))
    }
  }
}
```

Dataset Cleansing Code

```
#########################################################################
### RUN THIS FILE FIRST
#########################################################################

library(plyr)
```

```
#setwd("C:/Users/Craig/Google Drive/Grad School/Harvard/Research/Hypertension/Data Pull") # Use
for PC version
if((Sys.info()["nodename"]) == "MacBook-Pro-4" | (Sys.info()["nodename"]) == "MacBook-Pro-
4.local" | (Sys.info()["nodename"]) == "Craig-Macbook-Pro-Ethernet")
{
  setwd("/Users/craigwhite3/Google Drive/Grad School/Harvard/Research/Hypertension/Data Pull/") #
use for Macbook Pro
} else {setwd("/Users/craigwhite/Google Drive/Grad School/Harvard/Research/Hypertension/Data
Pull/")} # use for Macbook 12"

################################################################################
# Load Functions from Other Files
################################################################################
if(!exists("generate_predictions", mode="function")) source("Hypertension_Functions.R")


################################################################################
# Global Variables Definitions
################################################################################
SBP_threshold_upper <- 144 # For the threshold analysis, upper limit on SBP
SBP_threshold_lower <- 135 # For the threshold analysis, lower limit on SBP
DBP_threshold_upper <- 92
DBP_threshold_lower <- 86
max_systolic_value <- 200
min_systolic_value <- 100
min_diastolic_value <- 55
max_diastolic_value <- 125
SBP_DBP_gap <- 10 # how far apart must the patient's SBP and DBP be to be a valid reading. e.g.
SBP must be 10mm higher than DBP
samplesize <- NULL # Set this to the size of the sample desired for regression models. Set to
NULL to use entire dataset.
Use_GP_Only = TRUE
################################################################################
GenerateCorrelationPlots <- RunROCCurve <- StartNew <- 'n'

#StartNew <- tolower(StartNew <- readline("Delete all existing data - start fresh? y/n:  "))
#RunROCCurve <- tolower(RunROCCurve <- readline(" Do you want to generate ROC curves? \n THIS CAN
TAKE A LONG TIME! y/n:  "))
#GenerateCorrelationPlots <- tolower(GenerateCorrelationPlots <- readline("Do you want to
generate correlation plots? \ This will show the aggregate correlation between even and odd BP
reports \n y/n:  "))

# Data file was modified within Oracle and using a sample (either 2%, 5%, 10% or 25%)
# Read in Data and select the patients we want to keep
NewDatasetCreated <- "FALSE"
if(!exists("Hyp") | StartNew == 'y')
{
  if(!exists("Hyp_Raw") | StartNew == 'y')
  {
    # Take a smaple from this if you want a smaller dataset
    Hyp_Raw <- read.csv('Hypertension Data Sample 100pc - NEW - BMI.csv') # 25% Sample -
14,750,387
  }
  # Create a clean master dataset by dropping incomplete cases, weird blood pressure readings and
patients who are already on medications for HT
  # Hyp_Raw <- cbind("generated_uid3" = sprintf("%03d", 1:nrow(Hyp_Raw)), Hyp_Raw)
  Hyp <- Hyp_Raw[complete.cases(Hyp_Raw[,c(1, 3)]),] # keep only records where there is a
systolic and diastolic BP - 14,733,003
  Hyp$BP_OBS_DATE <- as.Date(Hyp$BP_OBS_DATE, "%d-%b-%y") # Convert the observation date to a
date type
  #Hyp <- na.omit(Hyp[Hyp$BP_OBS_DATE < as.Date("2013-12-17"),]) # Drop any observations that
were after the JNC8 guidelines came into effect
  Hyp <- Hyp[Hyp$SYSTOLIC_VALUE <= max_systolic_value & Hyp$SYSTOLIC_VALUE > min_systolic_value &
Hyp$DIASTOLIC_VALUE > min_diastolic_value & Hyp$DIASTOLIC_VALUE <= max_diastolic_value,] # -
13,721,016
  Hyp <- Hyp[(Hyp$DIASTOLIC_VALUE+SBP_DBP_gap < Hyp$SYSTOLIC_VALUE),] # Drop records where the
systolic is not 10mmHg greater than the diastolic value (n=1) - 13,720,453
  Hyp <- Hyp[Hyp$ON_EXISTING_HT_MEDICATION == 0,] # Drop any record where patient is already
being treated for HT - 21,113,985

  NewDatasetCreated <- TRUE
}
```

```
#####################################################################
### CREATE NEW VARIABLES for Regression Models
### Flag patients who have any of the labeled comorbidities (Diabetes, CVA, IHD, MI, PVD, CHF)
### CREATE THE LABELS for all the numeric coding
### This is useful for the regression covariates labeling
#####################################################################
if (NewDatasetCreated == TRUE)
{
  Hyp$HasComorbidities <- (Hyp$DIABETIC_DURING_VISIT + Hyp$HIST_CVA_DURING_VISIT +
Hyp$HIST_IHD_DURING_VISIT + Hyp$HIST_MI_DURING_VISIT + Hyp$HIST_PVD_DURING_VISIT +
Hyp$HIST_CHF_DURING_VISIT) > 0
# Create the rounded versions of the BP values for "bucketing" to deal with the oscillations in
probability
  Hyp$SYSTOLIC_VALUE_RND2 <- as.integer(round_any(Hyp$SYSTOLIC_VALUE, 2, floor))
  Hyp$DIASTOLIC_VALUE_RND2 <- as.integer(round_any(Hyp$DIASTOLIC_VALUE, 2, floor))
# Flag even and odd records to use it in the regression (instead of bucketing)
  Hyp$EVEN_SYSTOLIC <- 1 - Hyp$SYSTOLIC_VALUE %% 2
  Hyp$EVEN_DIASTOLIC <- 1 - Hyp$DIASTOLIC_VALUE %% 2 # Create a new variable
  systolic_pct_even <- mean(Hyp$EVEN_SYSTOLIC)
  diastolic_pct_even <- mean(Hyp$EVEN_DIASTOLIC)
  Hyp$Zero_End_Digit_Systolic <-  Hyp$SYSTOLIC_VALUE %% 10 == 0
  Hyp$Zero_End_Digit_Diastolic <- Hyp$DIASTOLIC_VALUE %% 10 == 0
  systolic_zero_end_digit <- mean(Hyp$Zero_End_Digit_Systolic)
  diastolic_zero_end_digit <- mean(Hyp$Zero_End_Digit_Diastolic)
# Integer value of the % of this physician's readings that are even for systolic and diastolic
  Hyp$PHYS_PCT_SYS_EVEN <- Hyp$PHYS_PROB_SYS_EVEN*100 # Variable showing for this physician what
their % of even systolic readings in the dataset is
  Hyp$PHYS_PCT_DIA_EVEN <- Hyp$PHYS_PROB_DIA_EVEN*100 # Variable showing for this physician what
their % of even diastolic readings in the dataset is
# Create Factor variables with appropriate cutpoints
  Hyp$AGE_ON_OBS_DATE <- cut(Hyp$AGE_ON_OBS_DATE, breaks = c(17, 30, 40, 50, 60, 70, 80, Inf),
labels = c("Age 18-30", "Age 30-40", "Age 40-50", "Age 50-60", "Age 60-70", "Age 70-80", "Age
80+"))
  Hyp$SYSTOLIC_VALUE_5MM <- cut(Hyp$SYSTOLIC_VALUE, breaks = seq(100, 200, 5), labels = c("SBP
100-104", "SBP 105-109", "SBP 110-114", "SBP 115-119", "SBP 120-124", "SBP 125-129", "SBP 130-
134", "SBP 135-139", "SBP 140-144", "SBP 145-149", "SBP 150-154", "SBP 155-159", "SBP 160-164",
"SBP 165-169", "SBP 170-174", "SBP 175-179", "SBP 180-184", "SBP 185-189", "SBP 190-194", "SBP
195-199"), ordered_result = FALSE, right = FALSE)
  Hyp$DIASTOLIC_VALUE_5MM <- cut(Hyp$DIASTOLIC_VALUE, breaks = seq(55, 125, 5), labels = c("DBP
55-59", "DBP 60-64", "DBP 65-69", "DBP 70-74", "DBP 75-79", "DBP 80-84", "DBP 85-89", "DBP 90-
94", "DBP 95-99", "DBP 100-104", "BP 105-109", "BP 110-114", "BP 115-119", "BP 120-124"),
ordered_result = FALSE, right = FALSE)
  Hyp$SYSTOLIC_VALUE_10MM <- cut(Hyp$SYSTOLIC_VALUE, breaks = seq(100, 200, 10), labels = c("SBP
100-109", "SBP 110-119", "SBP 120-129", "SBP 130-139", "SBP 140-149", "SBP 150-159","SBP 160-
169","SBP 170-179", "SBP 180-189", "SBP 190-199"), ordered_result = FALSE, right = FALSE)
  Hyp$DIASTOLIC_VALUE_10MM <- cut(Hyp$DIASTOLIC_VALUE, breaks = seq(55, 125, 10), labels = c("DBP
55-64", "DBP 65-74", "DBP 75-84", "DBP 85-94", "DBP 95-104", "BP 105-114", "BP 115-124"),
ordered_result = FALSE, right = FALSE)


  # Label and reformat existing variables
  Hyp$IS_PHYSICIAN_CODE <- factor(Hyp$IS_PHYSICIAN_CODE, levels = c(0,1), labels = c("Non-
Physician", "Physician"))
  Hyp$PATIENT_GENDER_CODE <- factor(Hyp$PATIENT_GENDER_CODE, levels = c("0", "1"), labels =
c("Male", "Female"))
  Hyp$PATIENT_RACE_CODE <- factor(Hyp$PATIENT_RACE_CODE, levels = c("0", "1", "2", "3", "4", "9",
"99"), labels = c("White", "Black","Asian","Native-American","Hawaii/Pac. Island", "Unknown",
"Not-Entered"))
  Hyp$PATIENT_ETHNICITY_CODE <- factor(Hyp$PATIENT_ETHNICITY_CODE, levels = c("0", "1", "9",
"99"), labels = c("Non-Hispanic", "Hispanic", "Unknown", "Not Entered"))
  Hyp$PATIENT_MARITAL_STATUS_CODE <- factor(Hyp$PATIENT_MARITAL_STATUS_CODE, levels = c("0", "1",
"2", "3", "4", "5", "9", "99"), labels = c("Married", "Single", "Widowed/Widower", "Divorced",
"Separated", "Partnered", "Unknown", "Not-Entered"))
  Hyp$PATIENT_EMPLOYMENT_STATUS_CODE <- factor(Hyp$PATIENT_EMPLOYMENT_STATUS_CODE, levels =
c("0", "1", "2", "9", "99"), labels = c("Unemployed", "Employed", "Retired", "Unknown", "Not-
Entered"))
  Hyp$EVEN_SYSTOLIC <- factor(Hyp$EVEN_SYSTOLIC, levels = c(0,1), labels = c("Odd", "Even"))
  Hyp$EVEN_DIASTOLIC <- factor(Hyp$EVEN_DIASTOLIC, levels = c(0,1), labels = c("Odd", "Even"))
  Hyp$SHOULD_BE_TREATED <- factor(Hyp$SHOULD_BE_TREATED, levels = c(0,1), labels = c("No",
"Yes"))
  Hyp$HasComorbidities <- factor(Hyp$HasComorbidities, levels = c('FALSE','TRUE'), labels =
c("FALSE", "TRUE"))
```

```
  Hyp$Phys_Specialty <- factor(Hyp$PROVIDER_SPECIALTY)
}
if(Use_GP_Only == TRUE) # If we want to use GP data only - This will go away if I have to run the
SQL again, since non-GPs will be removed in SQL
{
  Hyp <- Hyp[Hyp$Phys_Specialty %in% c("internal medicine", "family practice", "cardiology"),]
}

#############################################################################################
### Mosaic display of the BP data with Friendly-like
### color coding of the residuals
#####################################################################
# - Odd and Even correlation check ----------------------------------#
if(GenerateCorrelationPlots == 'y')
{
  Hyp_Cor_Data <- Hyp[,c("SYSTOLIC_VALUE", "EVEN_SYSTOLIC","DIASTOLIC_VALUE", "EVEN_DIASTOLIC")]
  Hyp_Cor_Data <- Hyp_Cor_Data[complete.cases(Hyp_Cor_Data),c("EVEN_DIASTOLIC", "EVEN_SYSTOLIC")]
  set.seed(1071)
  BP_chisq <- coindep_test(table(Hyp_Cor_Data), indepfun = function(x) sum(x^2))
  labs <- round(prop.table(table(Hyp_Cor_Data)), 3)
  mosaic(table(Hyp_Cor_Data), pop = FALSE, colorize = TRUE,
labeling_args=list(gp_labels=(gpar(fontsize=14))))
  labeling_cells(text = labs, margin = 0, fontsize = 20) (table(Hyp_Cor_Data))
}
```

Hypertension Regression Models

```
# Load Packages
library(arm)
library(MASS)
library(stats)
library(vcd)
library(utils)
library(car)

library(speedglm)
library(xlsx) # For writing output files to Excel
library(caret) # For creating testing and training datasets
#library(effects) # Used for plotting effects, but only works for GLM, not SpeedGLM?

#####################################################################
###
### ------- Analyze using some Logistic models --------------#
### Specify the models
#####################################################################
options(scipen = 10) # Make sure coefficients show without scientific notation

# Regression Model specifications
reg_formula_systolic_simple <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE*SHOULD_BE_TREATED
reg_formula_diastolic_simple <- ANTIHYPERTENSIVE_PRESCRIBED ~ DIASTOLIC_VALUE*SHOULD_BE_TREATED

reg_formula_systolic <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE*SHOULD_BE_TREATED +
EVEN_SYSTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE + HasComorbidities
reg_formula_diastolic <- ANTIHYPERTENSIVE_PRESCRIBED ~ DIASTOLIC_VALUE*SHOULD_BE_TREATED +
EVEN_DIASTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE + HasComorbidities

reg_formula_systolic_5mm <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE_5MM + SHOULD_BE_TREATED
+ EVEN_SYSTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE + HasComorbidities
reg_formula_diastolic_5mm <- ANTIHYPERTENSIVE_PRESCRIBED ~ DIASTOLIC_VALUE_5MM +
SHOULD_BE_TREATED + EVEN_SYSTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE + HasComorbidities

reg_formula_systolic_10mm <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE_10MM +
SHOULD_BE_TREATED + EVEN_SYSTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
```

```
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE + HasComorbidities
reg_formula_diastolic_10mm <- ANTIHYPERTENSIVE_PRESCRIBED ~ DIASTOLIC_VALUE_10MM +
SHOULD_BE_TREATED + EVEN_SYSTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE + HasComorbidities

# Subgroup Regression Model Specifications
reg_formula_gender   <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE*SHOULD_BE_TREATED +
EVEN_SYSTOLIC + IS_PHYSICIAN_CODE +                         PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE + HasComorbidities
reg_formula_comorbid <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE*SHOULD_BE_TREATED +
EVEN_SYSTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE
reg_formula_age      <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE*SHOULD_BE_TREATED +
EVEN_SYSTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI +                   HasComorbidities
reg_formula_race     <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE*SHOULD_BE_TREATED +
EVEN_SYSTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + AGE_ON_OBS_DATE + HasComorbidities

reg_formula_age_diastolic      <- ANTIHYPERTENSIVE_PRESCRIBED ~ DIASTOLIC_VALUE*SHOULD_BE_TREATED
+ EVEN_DIASTOLIC + IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE +
PATIENT_ETHNICITY_CODE + PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE +
PATIENT_BMI + HasComorbidities

# Models for the threshold analyses

Hyp_Sys_Threshold_SBP <- Hyp[Hyp$SYSTOLIC_VALUE < SBP_threshold_upper & Hyp$SYSTOLIC_VALUE >
SBP_threshold_lower,]
reg_formula_sys_threshold <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE_5MM + SHOULD_BE_TREATED
+ IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE + PATIENT_ETHNICITY_CODE +
PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE + PATIENT_BMI + AGE_ON_OBS_DATE +
HasComorbidities

##############################################################################################
# ------------------------------- Overall Analysis ----------------------------------#
##############################################################################################
####################--------------- Whole Population ----------------------##############
##############################################################################################
# Create a dataset for regression model and run the regressions on it, then predictions
if(is.null(samplesize))
{
  Hyp_Sample <- Hyp
}
if(!is.null(samplesize) && exists("Hyp_Sample"))
{
  if(max(nrow((Hyp_Sample)) != samplesize))
  {
    Hyp_Sample <- Hyp[sample(1:nrow(Hyp), samplesize, replace = FALSE),] # Use a sample to avoid
crashing my machine
  }
}
if(!is.null(samplesize) && !exists("Hyp_Sample"))
{
  Hyp_Sample <- Hyp[sample(1:nrow(Hyp), samplesize, replace = FALSE),]
}
Hyp_Sample <- na.exclude(Hyp_Sample)

glm.fit.systolic <- run_logistic_regression(reg_eqn = reg_formula_systolic, dataset = Hyp_Sample,
regression_name = "Sys Overall Pop")
glm.fit.systolic_simple <- run_logistic_regression(reg_eqn = reg_formula_systolic_simple, dataset
= Hyp_Sample, regression_name = "Overall SBP Pop")
glm.fit.systolic_5mm <- run_logistic_regression(reg_eqn = reg_formula_systolic_5mm, dataset =
Hyp_Sample, regression_name = "Overall-SBP 5mm")
glm.fit.systolic_10mm <- run_logistic_regression(reg_eqn = reg_formula_systolic_10mm, dataset =
Hyp_Sample, regression_name = "Overall-SBP 10mm")
```

```
Hyp_Sample$fitted.glm.fit.systolic <- fitted(glm.fit.systolic)
Hyp_Sample$fitted.glm.fit.systolic_5mm <- fitted(glm.fit.systolic_5mm)
Hyp_Sample$fitted.glm.fit.systolic_10mm <- fitted(glm.fit.systolic_10mm)


glm.fit.diastolic <- run_logistic_regression(reg_eqn = reg_formula_diastolic, dataset =
Hyp_Sample, regression_name = "Dia Overall Pop")
glm.fit.diastolic_simple <- run_logistic_regression(reg_eqn = reg_formula_diastolic_simple,
dataset = Hyp_Sample, regression_name = "Overall DBP Pop")
glm.fit.diastolic_5mm <- run_logistic_regression(reg_eqn = reg_formula_diastolic_5mm, dataset =
Hyp_Sample, regression_name = "Overall - DBP 5mm")
glm.fit.diastolic_10mm <- run_logistic_regression(reg_eqn = reg_formula_diastolic_10mm, dataset =
Hyp_Sample, regression_name = "Overall - DBP 10mm")

predictions_5mm <- data.frame(SBP_Range = seq(101,200, 5))
predictions_5mm$All_Patients_Actual <- tapply(Hyp_Sample$ANTIHYPERTENSIVE_PRESCRIBED,
Hyp_Sample$SYSTOLIC_VALUE_5MM, mean) # All patients
predictions_5mm$All_Patients_Model <- tapply(Hyp_Sample$fitted.glm.fit.systolic_5mm,
Hyp_Sample$SYSTOLIC_VALUE_5MM, mean) # All patients
predictions_5mm$White_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White",]$SYSTOLIC_VALUE_5MM, mean) # White patients
predictions_5mm$Black_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black",]$SYSTOLIC_VALUE_5MM, mean) # Black patients
predictions_5mm$Asian_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian",]$SYSTOLIC_VALUE_5MM, mean) # Asian patients
predictions_5mm$Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE_5MM, mean) # Male patients
predictions_5mm$Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE_5MM, mean) # Female patients
predictions_5mm$Comorbid_Patients <- tapply(Hyp_Sample[Hyp_Sample$HasComorbidities ==
"TRUE",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$HasComorbidities ==
"TRUE",]$SYSTOLIC_VALUE_5MM, mean) # Comorbid patients
predictions_5mm$Healthy_Patients <- tapply(Hyp_Sample[Hyp_Sample$HasComorbidities ==
"FALSE",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$HasComorbidities ==
"FALSE",]$SYSTOLIC_VALUE_5MM, mean) # Comorbid patients
predictions_5mm$White_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic_5mm,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE_5MM, mean) # White patients
predictions_5mm$Black_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic_5mm,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE_5MM, mean) # Black patients
predictions_5mm$Asian_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic_5mm,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE_5MM, mean) # Asian patients
predictions_5mm$White_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic_5mm,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE_5MM, mean) # White patients
predictions_5mm$Black_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic_5mm,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE_5MM, mean) # Black patients
predictions_5mm$Asian_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic_5mm,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE_5MM, mean) # Asian patients
predictions_5mm$Age18_30_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 18-
30",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 18-
30",]$SYSTOLIC_VALUE_5MM, mean) # 18-30 patients
predictions_5mm$Age30_40_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 30-
40",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 30-
40",]$SYSTOLIC_VALUE_5MM, mean) # 30-40 patients
predictions_5mm$Age40_50_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 40-
50",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 40-
50",]$SYSTOLIC_VALUE_5MM, mean) # 40-50 patients
```

```
predictions_5mm$Age50_60_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 50-
60",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 50-
60",]$SYSTOLIC_VALUE_5MM, mean) # 50-60 patients
predictions_5mm$Age60_70_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 60-
70",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 60-
70",]$SYSTOLIC_VALUE_5MM, mean) # 60-70 patients
predictions_5mm$Age70_80_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 70-
80",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 70-
80",]$SYSTOLIC_VALUE_5MM, mean) # 70-80 patients
predictions_5mm$Age80_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age
80+",]$fitted.glm.fit.systolic_5mm, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age
80+",]$SYSTOLIC_VALUE_5MM, mean) # 80+ patients
Today <- format(Sys.time(), format="%B %d %Y %H-%M")
xls_filename <- paste0('Hypertension Regression Prediction Outputs Auto Generated Sample
',Today,'.xlsx', sep="")
prediction_name <- "Predictions 5mm Model"
write.xlsx(predictions_5mm, xls_filename, paste(prediction_name,' n=', nrow(Hyp_Sample), sep =
""), append = TRUE)

predictions_10mm <- data.frame(SBP_Range = seq(101,200, 10))
predictions_10mm$All_Patients_Actual <- tapply(Hyp_Sample$ANTIHYPERTENSIVE_PRESCRIBED,
Hyp_Sample$SYSTOLIC_VALUE_10MM, mean) # All patients
predictions_10mm$All_Patients_Model <- tapply(Hyp_Sample$fitted.glm.fit.systolic_10MM,
Hyp_Sample$SYSTOLIC_VALUE_10MM, mean) # All patients
predictions_10mm$White_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White",]$SYSTOLIC_VALUE_10MM, mean) # White patients
predictions_10mm$Black_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black",]$SYSTOLIC_VALUE_10MM, mean) # Black patients
predictions_10mm$Asian_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian",]$SYSTOLIC_VALUE_10MM, mean) # Asian patients
predictions_10mm$Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE_10MM, mean) # Male patients
predictions_10mm$Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE_10MM, mean) # Female patients
predictions_10mm$Comorbid_Patients <- tapply(Hyp_Sample[Hyp_Sample$HasComorbidities ==
"TRUE",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$HasComorbidities ==
"TRUE",]$SYSTOLIC_VALUE_10MM, mean) # Comorbid patients
predictions_10mm$Healthy_Patients <- tapply(Hyp_Sample[Hyp_Sample$HasComorbidities ==
"FALSE",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$HasComorbidities ==
"FALSE",]$SYSTOLIC_VALUE_10MM, mean) # Comorbid patients
predictions_10mm$White_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic_10MM,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE_10MM, mean) # White patients
predictions_10mm$Black_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic_10MM,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE_10MM, mean) # Black patients
predictions_10mm$Asian_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic_10MM,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE_10MM, mean) # Asian patients
predictions_10mm$White_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic_10MM,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE_10MM, mean) # White patients
predictions_10mm$Black_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic_10MM,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE_10MM, mean) # Black patients
predictions_10mm$Asian_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic_10MM,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE_10MM, mean) # Asian patients
predictions_10mm$Age18_30_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 18-
30",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 18-
30",]$SYSTOLIC_VALUE_10MM, mean) # 18-30 patients
```

```
predictions_10mm$Age30_40_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 30-
40",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 30-
40",]$SYSTOLIC_VALUE_10MM, mean) # 30-40 patients
predictions_10mm$Age40_50_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 40-
50",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 40-
50",]$SYSTOLIC_VALUE_10MM, mean) # 40-50 patients
predictions_10mm$Age50_60_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 50-
60",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 50-
60",]$SYSTOLIC_VALUE_10MM, mean) # 50-60 patients
predictions_10mm$Age60_70_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 60-
70",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 60-
70",]$SYSTOLIC_VALUE_10MM, mean) # 60-70 patients
predictions_10mm$Age70_80_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 70-
80",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 70-
80",]$SYSTOLIC_VALUE_10MM, mean) # 70-80 patients
predictions_10mm$Age80_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age
80+",]$fitted.glm.fit.systolic_10MM, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age
80+",]$SYSTOLIC_VALUE_10MM, mean) # 80+ patients
Today <- format(Sys.time(), format="%B %d %Y %H-%M")
xls_filename <- paste0('Hypertension Regression Prediction Outputs Auto Generated Sample
',Today,'.xlsx', sep="")
prediction_name <- "Predictions 10mm Model"
write.xlsx(predictions_10mm, xls_filename, paste(prediction_name,' n=', nrow(Hyp_Sample), sep =
""), append = TRUE)

predictions_1mm <- data.frame(SBP_Range = seq(101,199, 1))
predictions_1mm$All_Patients_Actual <- tapply(Hyp_Sample$ANTIHYPERTENSIVE_PRESCRIBED,
Hyp_Sample$SYSTOLIC_VALUE, mean) # All patients
predictions_1mm$All_Patients_Model <- tapply(Hyp_Sample$fitted.glm.fit.systolic,
Hyp_Sample$SYSTOLIC_VALUE, mean) # All patients
predictions_1mm$White_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White",]$SYSTOLIC_VALUE, mean) # White patients
predictions_1mm$Black_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black",]$SYSTOLIC_VALUE, mean) # Black patients
predictions_1mm$Asian_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian",]$SYSTOLIC_VALUE, mean) # Asian patients
predictions_1mm$Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE, mean) # Male patients
predictions_1mm$Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE, mean) # Female patients
predictions_1mm$Comorbid_Patients <- tapply(Hyp_Sample[Hyp_Sample$HasComorbidities ==
"TRUE",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$HasComorbidities ==
"TRUE",]$SYSTOLIC_VALUE, mean) # Comorbid patients
predictions_1mm$Healthy_Patients <- tapply(Hyp_Sample[Hyp_Sample$HasComorbidities ==
"FALSE",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$HasComorbidities ==
"FALSE",]$SYSTOLIC_VALUE, mean) # Comorbid patients
predictions_1mm$White_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE, mean) # White patients
predictions_1mm$Black_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE, mean) # Black patients
predictions_1mm$Asian_Male_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian"
& Hyp_Sample$PATIENT_GENDER_CODE == "Male",]$fitted.glm.fit.systolic,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Male",]$SYSTOLIC_VALUE, mean) # Asian patients
predictions_1mm$White_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"White" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "White" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE, mean) # White patients
predictions_1mm$Black_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Black" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic,
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Black" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE, mean) # Black patients
predictions_1mm$Asian_Female_Patients <- tapply(Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE ==
"Asian" & Hyp_Sample$PATIENT_GENDER_CODE == "Female",]$fitted.glm.fit.systolic,
```

```
Hyp_Sample[Hyp_Sample$PATIENT_RACE_CODE == "Asian" & Hyp_Sample$PATIENT_GENDER_CODE ==
"Female",]$SYSTOLIC_VALUE, mean) # Asian patients
predictions_1mm$Age18_30_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 18-
30",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 18-
30",]$SYSTOLIC_VALUE, mean) # 18-30 patients
predictions_1mm$Age30_40_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 30-
40",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 30-
40",]$SYSTOLIC_VALUE, mean) # 30-40 patients
predictions_1mm$Age40_50_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 40-
50",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 40-
50",]$SYSTOLIC_VALUE, mean) # 40-50 patients
predictions_1mm$Age50_60_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 50-
60",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 50-
60",]$SYSTOLIC_VALUE, mean) # 50-60 patients
predictions_1mm$Age60_70_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 60-
70",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 60-
70",]$SYSTOLIC_VALUE, mean) # 60-70 patients
predictions_1mm$Age70_80_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 70-
80",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age 70-
80",]$SYSTOLIC_VALUE, mean) # 70-80 patients
predictions_1mm$Age80_Patients <- tapply(Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age
80+",]$fitted.glm.fit.systolic, Hyp_Sample[Hyp_Sample$AGE_ON_OBS_DATE == "Age
80+",]$SYSTOLIC_VALUE, mean) # 80+ patients
prediction_name <- "Predictions 1mm Model"
write.xlsx(predictions_1mm, xls_filename, paste(prediction_name,' n=', nrow(Hyp_Sample), sep =
""), append = TRUE)

rm(glm.fit.systolic)
rm(glm.fit.systolic_simple) # remove the glm objects
rm(glm.fit.systolic_5mm)
rm(glm.fit.systolic_10mm)

rm(glm.fit.diastolic)
rm(glm.fit.diastolic_simple) # remove the glm objects
rm(glm.fit.diastolic_5mm)
rm(glm.fit.daistolic_10mm)
gc() # garbage collection to free up memory

##############################################################################
# ------------------ Subgroup Analyses by Age, Sex, Comobrbidities ----------------#
##############################################################################
####################---------------- FEMALE ----------------------#################
# Get the dataset
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Female <- Hyp[Hyp$PATIENT_GENDER_CODE == "Female",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Female"))
{
  if(max(nrow((Hyp_Reg_Naive_Female)) != samplesize))
  { Hyp_Reg_Naive_Female <- Hyp[sample(1:nrow(subset(Hyp, Hyp$PATIENT_GENDER_CODE == "Female")),
samplesize, replace = FALSE),] }
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Female"))
{
  Hyp_Reg_Naive_Female <- Hyp[sample(1:nrow(subset(Hyp, Hyp$PATIENT_GENDER_CODE == "Female")),
samplesize, replace = FALSE),]
}
Hyp_Reg_Naive_Female <- na.exclude(Hyp_Reg_Naive_Female)

# Run the regression

glm.fit.systolic.female <- run_logistic_regression(reg_eqn = reg_formula_gender, dataset =
Hyp_Reg_Naive_Female, regression_name = "Gender Female")
Hyp_Reg_Naive_Female$fitted.glm.fit.systolic.female <- fitted(glm.fit.systolic.female)
#Master_data <- merge(Hyp_Sample, Hyp_Reg_Naive_Female, by = "row.names", all.x = TRUE)
# Clean up and free memory
rm(glm.fit.systolic.female)
gc() # garbage collection to free up memory

####################---------------- MALE ----------------------#################
# Get the data
if(is.null(samplesize))
```

```
{
  Hyp_Reg_Naive_Male <- Hyp[Hyp$PATIENT_GENDER_CODE == "Male",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Male"))
{
  if(max(nrow((Hyp_Reg_Naive_Male)) != samplesize))
  { Hyp_Reg_Naive_Male <- Hyp[sample(1:nrow(subset(Hyp, Hyp$PATIENT_GENDER_CODE == "Male")),
samplesize, replace = FALSE),] }
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Male"))
{
  Hyp_Reg_Naive_Male <- Hyp[sample(1:nrow(subset(Hyp, Hyp$PATIENT_GENDER_CODE == "Male")),
samplesize, replace = FALSE),]
}
Hyp_Reg_Naive_Male <- na.exclude(Hyp_Reg_Naive_Male)
glm.fit.systolic.male <- run_logistic_regression(reg_eqn = reg_formula_gender, dataset =
Hyp_Reg_Naive_Male, regression_name = "Gender Male")
#generate_predictions(glm.fit.systolic.male)

rm(glm.fit.systolic.male)
gc() # garbage collection to free up memory

####################---------------- COMORBID ----------------------#################
# Get the data
if(is.null(samplesize))
{ Hyp_Reg_Naive_Comorbid_Patients <- Hyp[Hyp$HasComorbidities == "TRUE",] }
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Comorbid_Patients"))
{ if(max(nrow((Hyp_Reg_Naive_Comorbid_Patients)) != samplesize))
{ Hyp_Reg_Naive_Comorbid_Patients <- Hyp[sample(1:nrow(subset(Hyp, Hyp$HasComorbidities ==
"TRUE")), samplesize, replace = FALSE),] }
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Comorbid_Patients"))
{ Hyp_Reg_Naive_Comorbid_Patients <- Hyp[sample(1:nrow(subset(Hyp, Hyp$HasComorbidities ==
"TRUE")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Comorbid_Patients <- na.exclude(Hyp_Reg_Naive_Comorbid_Patients)
# Run the regression
glm.fit.systolic.comorbid <- run_logistic_regression(reg_eqn = reg_formula_comorbid, dataset =
Hyp_Reg_Naive_Comorbid_Patients, regression_name = "Comorbid Patients")
#generate_predictions(glm.fit.systolic.comorbid)
# Write the output to a file
rm(glm.fit.systolic.comorbid)
gc() # garbage collection to free up memory

####################---------------- HEALTHY ----------------------#################
# Get the data
if(is.null(samplesize))
{
  Hyp_Reg_Naive_OtherwiseHealthy_Patients <- Hyp[Hyp$HasComorbidities == "FALSE",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_OtherwiseHealthy_Patients"))
{
  if(max(nrow((Hyp_Reg_Naive_OtherwiseHealthy_Patients)) != samplesize))
  {Hyp_Reg_Naive_OtherwiseHealthy_Patients <- Hyp[sample(1:nrow(subset(Hyp, Hyp$HasComorbidities
== "FALSE")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_OtherwiseHealthy_Patients"))
{ Hyp_Reg_Naive_OtherwiseHealthy_Patients <- Hyp[sample(1:nrow(subset(Hyp, Hyp$HasComorbidities
== "FALSE")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_OtherwiseHealthy_Patients <- na.exclude(Hyp_Reg_Naive_OtherwiseHealthy_Patients)
# Run the regression
glm.fit.systolic.healthy <- run_logistic_regression(reg_eqn = reg_formula_comorbid, dataset =
Hyp_Reg_Naive_OtherwiseHealthy_Patients, regression_name = "Healthy Patients")
#generate_predictions(glm.fit.systolic.healthy)
rm(glm.fit.systolic.healthy)
gc() # garbage collection to free up memory

####################---------------- Age Analyses ----------------#################
####################---------------- 18 - 30 ----------------------#################
# Could do this as a loop using the factor (e.g. for(x = 1 to 5), then set the factor
# to be a subset of the master dataset (e.g. Hyp[Hyp$AGE_ON_OBS_DATE == x]))
# Get the data

#-------------------------------------------------------------------------------#
```

```
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Patients_Age18_30 <- Hyp[Hyp$AGE_ON_OBS_DATE == "Age 18-30",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Patients_Age18_30"))
{
  if(max(nrow((Hyp_Reg_Naive_Patients_Age18_30)) != samplesize))
  {Hyp_Reg_Naive_Patients_Age18_30 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
18-30")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Patients_Age18_30"))
{ Hyp_Reg_Naive_Patients_Age18_30 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
18-30")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Patients_Age18_30 <- na.exclude(Hyp_Reg_Naive_Patients_Age18_30)
# Run the regression
glm.fit.systolic.18_30 <- run_logistic_regression(reg_eqn = reg_formula_age, dataset =
Hyp_Reg_Naive_Patients_Age18_30, regression_name = "18_30yo Patients")
glm.fit.diastolic.18_30 <- run_logistic_regression(reg_eqn = reg_formula_age_diastolic, dataset =
Hyp_Reg_Naive_Patients_Age18_30, regression_name = "18_30yo Patients")

#generate_predictions(glm.fit.systolic.18_30)
rm(glm.fit.systolic.18_30)
gc() # garbage collection to free up memory

####################---------- 30 - 40 ----------####################
# Get the data
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Patients_Age30_40 <- Hyp[Hyp$AGE_ON_OBS_DATE == "Age 30-40",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Patients_Age30_40"))
{
  if(max(nrow((Hyp_Reg_Naive_Patients_Age30_40)) != samplesize))
  {Hyp_Reg_Naive_Patients_Age30_40 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
30-40")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Patients_Age30_40"))
{ Hyp_Reg_Naive_Patients_Age30_40 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
30-40")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Patients_Age30_40 <- na.exclude(Hyp_Reg_Naive_Patients_Age30_40)
# Run the regression
glm.fit.systolic.30_40 <- run_logistic_regression(reg_eqn = reg_formula_age, dataset =
Hyp_Reg_Naive_Patients_Age30_40, regression_name = "30-40yo Patients")
glm.fit.diastolic.30_40 <- run_logistic_regression(reg_eqn = reg_formula_age_diastolic, dataset =
Hyp_Reg_Naive_Patients_Age30_40, regression_name = "30_40yo Patients")

#generate_predictions(glm.fit.systolic.30_40)
rm(glm.fit.systolic.30_40)
gc() # garbage collection to free up memory

####################---------- 40 - 50 ----------####################
# Get the data
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Patients_Age40_50 <- Hyp[Hyp$AGE_ON_OBS_DATE == "Age 40-50",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Patients_Age40_50"))
{
  if(max(nrow((Hyp_Reg_Naive_Patients_Age40_50)) != samplesize))
  {Hyp_Reg_Naive_Patients_Age40_50 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
40-50")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Patients_Age40_50"))
{ Hyp_Reg_Naive_Patients_Age40_50 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
40-50")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Patients_Age40_50 <- na.exclude(Hyp_Reg_Naive_Patients_Age40_50)
# Run the regression
glm.fit.systolic.40_50 <- run_logistic_regression(reg_eqn = reg_formula_age, dataset =
Hyp_Reg_Naive_Patients_Age40_50, regression_name = "40-50yo Patients")
glm.fit.diastolic.40_50 <- run_logistic_regression(reg_eqn = reg_formula_age_diastolic, dataset =
Hyp_Reg_Naive_Patients_Age40_50, regression_name = "40_50yo Patients")

#generate_predictions(glm.fit.systolic.40_50)
```

```
rm(glm.fit.systolic.40_50)
gc() # garbage collection to free up memory

####################---------- 50 - 60 ----------####################
# Get the data
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Patients_Age50_60 <- Hyp[Hyp$AGE_ON_OBS_DATE == "Age 50-60",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Patients_Age50_60"))
{
  if(max(nrow((Hyp_Reg_Naive_Patients_Age50_60)) != samplesize))
  {Hyp_Reg_Naive_Patients_Age50_60 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
50-60")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Patients_Age50_60"))
{ Hyp_Reg_Naive_Patients_Age50_60 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
50-60")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Patients_Age50_60 <- na.exclude(Hyp_Reg_Naive_Patients_Age50_60)
# Run the regression
glm.fit.systolic.50_60 <- run_logistic_regression(reg_eqn = reg_formula_age, dataset =
Hyp_Reg_Naive_Patients_Age50_60, regression_name = "50_60yo Patients")
glm.fit.diastolic.50_60 <- run_logistic_regression(reg_eqn = reg_formula_age_diastolic, dataset =
Hyp_Reg_Naive_Patients_Age50_60, regression_name = "50_60yo Patients")

#generate_predictions(glm.fit.systolic.50_60)
rm(glm.fit.systolic.50_60)
gc() # garbage collection to free up memory

####################---------- 60 - 70 ----------####################
# Get the data
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Patients_Age60_70 <- Hyp[Hyp$AGE_ON_OBS_DATE == "Age 60-70",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Patients_Age60_70"))
{
  if(max(nrow((Hyp_Reg_Naive_Patients_Age60_70)) != samplesize))
  {Hyp_Reg_Naive_Patients_Age60_70 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
60-70")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Patients_Age60_70"))
{ Hyp_Reg_Naive_Patients_Age60_70 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
60-70")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Patients_Age60_70 <- na.exclude(Hyp_Reg_Naive_Patients_Age60_70)
# Run the regression
glm.fit.systolic.60_70 <- run_logistic_regression(reg_eqn = reg_formula_age, dataset =
Hyp_Reg_Naive_Patients_Age60_70, regression_name = "60-70yo Patients")
glm.fit.diastolic.60_70 <- run_logistic_regression(reg_eqn = reg_formula_age_diastolic, dataset =
Hyp_Reg_Naive_Patients_Age60_70, regression_name = "60_70yo Patients")

#generate_predictions(glm.fit.systolic.60_70)
rm(glm.fit.systolic.60_70)
gc() # garbage collection to free up memory

####################---------- 70 - 80 ----------####################
# Get the data
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Patients_Age70_80 <- Hyp[Hyp$AGE_ON_OBS_DATE == "Age 70-80",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Patients_Age70_80"))
{
  if(max(nrow((Hyp_Reg_Naive_Patients_Age70_80)) != samplesize))
  {Hyp_Reg_Naive_Patients_Age70_80 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
70-80")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Patients_Age70_80"))
{ Hyp_Reg_Naive_Patients_Age70_80 <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
70-80")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Patients_Age70_80 <- na.exclude(Hyp_Reg_Naive_Patients_Age70_80)
# Run the regression
```

```
glm.fit.systolic.70_80 <- run_logistic_regression(reg_eqn = reg_formula_age, dataset =
Hyp_Reg_Naive_Patients_Age70_80, regression_name = "70-80yo Patients")
glm.fit.diastolic.70_80 <- run_logistic_regression(reg_eqn = reg_formula_age_diastolic, dataset =
Hyp_Reg_Naive_Patients_Age70_80, regression_name = "70_80yo Patients")

#generate_predictions(glm.fit.systolic.70_80)
rm(glm.fit.systolic.70_80)
gc() # garbage collection to free up memory

####################---------------- 80+ --------------------##################
# Get the data
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Patients_Age80_ <- Hyp[Hyp$AGE_ON_OBS_DATE == "Age 80+",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Patients_Age80_"))
{
  if(max(nrow((Hyp_Reg_Naive_Patients_Age80_)) != samplesize))
  {Hyp_Reg_Naive_Patients_Age80_ <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
80+")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Patients_Age80_"))
{ Hyp_Reg_Naive_Patients_Age80_ <- Hyp[sample(1:nrow(subset(Hyp, Hyp$AGE_ON_OBS_DATE == "Age
80+")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Patients_Age80_ <- na.exclude(Hyp_Reg_Naive_Patients_Age80_)
# Run the regression
glm.fit.systolic.80_ <- run_logistic_regression(reg_eqn = reg_formula_age, dataset =
Hyp_Reg_Naive_Patients_Age80_, regression_name = "80+ yo Patients")
glm.fit.diastolic.80_ <- run_logistic_regression(reg_eqn = reg_formula_age_diastolic, dataset =
Hyp_Reg_Naive_Patients_Age80_, regression_name = "80+ yo Patients")

#generate_predictions(glm.fit.systolic.80_)
rm(glm.fit.systolic.80_)
gc() # garbage collection to free up memory

####################---------------- Black --------------------##################
# Get the data
if(is.null(samplesize))
{
  Hyp_Reg_Naive_Patients_Black <- Hyp[Hyp$PATIENT_RACE_CODE == "Black",]
}
if(!is.null(samplesize) && exists("Hyp_Reg_Naive_Patients_Black"))
{
  if(max(nrow((Hyp_Reg_Naive_Patients_Black)) != samplesize))
  {Hyp_Reg_Naive_Patients_Black <- Hyp[sample(1:nrow(subset(Hyp, Hyp$PATIENT_RACE_CODE ==
"Black")), samplesize, replace = FALSE),]}
}
if(!is.null(samplesize) && !exists("Hyp_Reg_Naive_Patients_Age80_"))
{ Hyp_Reg_Naive_Patients_Black <- Hyp[sample(1:nrow(subset(Hyp, Hyp$PATIENT_RACE_CODE ==
"Black")), samplesize, replace = FALSE),] }
Hyp_Reg_Naive_Patients_Black <- na.exclude(Hyp_Reg_Naive_Patients_Black)
# Run the regression
glm.fit.systolic.Black <- run_logistic_regression(reg_eqn = reg_formula_race, dataset =
Hyp_Reg_Naive_Patients_Black, regression_name = "Black Patients")
#generate_predictions(glm.fit.systolic.Black)
rm(glm.fit.systolic.Black)
gc() # garbage collection to free up memory
#############################################################################################
### Test a model where we only have patients with BP values near the threshold
### Include only those with SBP 135 - 145
###
#############################################################################################

Hyp_Threshold_SBP <- Hyp[Hyp$SYSTOLIC_VALUE <= SBP_threshold_upper & Hyp$SYSTOLIC_VALUE >=
SBP_threshold_lower & Hyp$DIABETIC_DURING_VISIT == FALSE,]
reg_formula_threshold_SBP <- ANTIHYPERTENSIVE_PRESCRIBED ~ SYSTOLIC_VALUE*SHOULD_BE_TREATED +
IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE + PATIENT_ETHNICITY_CODE +
PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE + PATIENT_BMI + AGE_ON_OBS_DATE +
HasComorbidities
# Run the regression
glm.fit.threshold_SBP <- run_logistic_regression(reg_eqn = reg_formula_threshold_SBP, dataset =
Hyp_Threshold_SBP, regression_name = "Threshold Analysis - SBP")
```

```
Hyp_Sys_Threshold_DBP <- Hyp[Hyp$DIASTOLIC_VALUE <= DBP_threshold_upper & Hyp$DIASTOLIC_VALUE >=
DBP_threshold_lower & Hyp$DIABETIC_DURING_VISIT == FALSE,]
reg_formula_threshold_DBP <- ANTIHYPERTENSIVE_PRESCRIBED ~ DIASTOLIC_VALUE*SHOULD_BE_TREATED +
IS_PHYSICIAN_CODE + PATIENT_GENDER_CODE + PATIENT_RACE_CODE + PATIENT_ETHNICITY_CODE +
PATIENT_MARITAL_STATUS_CODE + PATIENT_EMPLOYMENT_STATUS_CODE + PATIENT_BMI + AGE_ON_OBS_DATE +
HasComorbidities
glm.fit.threshold_DBP <- run_logistic_regression(reg_eqn = reg_formula_threshold_DBP, dataset =
Hyp_Sys_Threshold_DBP, regression_name = "Threshold Analysis - DBP")

#generate_predictions(glm.fit.threshold)
rm(glm.fit.threshold)
gc() # garbage collection to free up memory
```

Hypertension Table 1 Epidemiology Statistics

```
# Table 1: Epidemiology Stats.
# Need to show:
# 1) Gender Male vs. Female vs Unknown
# 2) Age buckets as reported in the regression (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+)
# 3) Marital Status by code (married, single, divorced, etc...)
# 4) Employment Status
# 5) Race Code (white, black, asian etc.)
# 6) Ethnicity Code (Hispanic, Non-Hispanic)
# 7) Comorbidities (Diabetes, MI, IHD, PVD, CHF)
install.packages("xtable")
library(xtable)
Table1Data <- Hyp_Raw
Table_1_Mean_SBP <- mean(Table1Data$SYSTOLIC_VALUE)
Table_1_SD_SBP <- sd(Table1Data$SYSTOLIC_VALUE)
Table_1_Mean_DBP <- mean(Table1Data$DIASTOLIC_VALUE)
Table_1_SD_DBP <- sd(Table1Data$DIASTOLIC_VALUE)
Table_1_Age_Dist <- prop.table(xtabs(~Table1Data$AGE_ON_OBS_DATE, data=Table1Data))
Table_1_Phys_Type <- prop.table(xtabs(~Table1Data$IS_PHYSICIAN_CODE, data=Table1Data))
tmp <- prop.table(xtabs(~Table1Data$PROVIDER_SPECIALTY))
Table_1_Phys_Specialty <- tmp[tmp>0.01]
Table_1_Gender <- prop.table(xtabs(~Table1Data$PATIENT_GENDER_CODE))
Table_1_Marital_Status <- prop.table(xtabs(~Table1Data$PATIENT_MARITAL_STATUS_CODE))
Table_1_Employment_Status <- prop.table(xtabs(~Table1Data$PATIENT_EMPLOYMENT_STATUS_CODE))
Table_1_Race <- prop.table(xtabs(~Table1Data$PATIENT_RACE_CODE))
Table_1_Ethnicity <- prop.table(xtabs(~Table1Data$PATIENT_ETHNICITY_CODE))
Table_1_Diabetes <- prop.table(xtabs(~Table1Data$DIABETIC_DURING_VISIT))
Table_1_MI <- prop.table(xtabs(~Table1Data$HIST_MI_DURING_VISIT))
Table_1_CVA <- prop.table(xtabs(~Table1Data$HIST_CVA_DURING_VISIT))
Table_1_IHD <- prop.table(xtabs(~Table1Data$HIST_IHD_DURING_VISIT))
Table_1_PVD <- prop.table(xtabs(~Table1Data$HIST_PVD_DURING_VISIT))
Table_1_CHF <- prop.table(xtabs(~Table1Data$HIST_CHF_DURING_VISIT))
Table_1_Physician <- prop.table(xtabs(~Table1Data$IS_PHYSICIAN_CODE))
Table_1_Sample_Size <- nrow(Table1Data)
```

Hypertension Descriptive Statistics

```
#########################################################################
### RUN THIS FILE AFTER THE HYPERTENSION REGRESSIONS FILE.
#########################################################################

# Load Packages
library(arm)
library(ggplot2)
library(stats)
library(ggfortify)
library(base)

Hyp_Diastolic <- read.csv('Probability of Prescription DIASTOLIC - NEW.csv')
Hyp_Systolic <- read.csv('Probability of Prescription SYSTOLIC - NEW.csv')
Hyp_Systolic_Diastolic <- read.csv('Probability of Prescription and Medication SYSTOLIC AND
DIASTOLIC - NEW.csv')
Hyp_Systolic_Diastolic <- Hyp_Systolic_Diastolic[complete.cases(Hyp_Systolic_Diastolic[,1:2]),]

#########################################################################
### Create the plots with separate regression lines for above and below
```

```
### threshold values of 90mmHg, 130mmHg and 140mmHg
### Do this for prescription probability only
### Show separate charts for diabetics and non-diabetics
### Only show for naive patients (e.g. those not already on therapy)
#########################################################################
# Plot the conditional Densities for Diastolic - Prescription
Hyp_Diastolic_No_Diab <- Hyp_Diastolic[Hyp_Diastolic$DIABETIC_DURING_VISIT == 0 &
Hyp_Diastolic$ON_EXISTING_HT_MEDICATION == 0,]
diastolic_plot_No_Diab <- ggplot(Hyp_Diastolic_No_Diab,
aes(Hyp_Diastolic_No_Diab$DIASTOLIC_VALUE, Hyp_Diastolic_No_Diab$PROBABILITY_OF_PRESCRIPTION,
color = factor(Hyp_Diastolic_No_Diab$SHOULD_BE_TREATED)))
diastolic_plot_No_Diab <- diastolic_plot_No_Diab + geom_point() + geom_vline(xintercept = 90,
linetype = "dashed", alpha = 0.6)
diastolic_plot_No_Diab <- diastolic_plot_No_Diab + ylab("Probability of Prescription")
diastolic_plot_No_Diab <- diastolic_plot_No_Diab + stat_smooth(method = "glm", method.args =
list(family = "gaussian", weights = as.vector(Hyp_Diastolic_No_Diab$N)), fullrange = FALSE, alpha
= 0.3) + stat_smooth(method = "glm", method.args = list(family = "gaussian"), fullrange = TRUE,
linetype = "dashed", lwd = 0.5, alpha = 0.15) + geom_point()
# diastolic_plot_No_Diab <- diastolic_plot_No_Diab + annotate("text", x = 75, y = 0.25, label =
lm_eqn(lm(Hyp_Diastolic_No_Diab$PROBABILITY~Hyp_Diastolic_No_Diab$DIASTOLIC_VALUE,
Hyp_Diastolic_No_Diab)), size = 3, parse=TRUE)
diastolic_plot_No_Diab <- diastolic_plot_No_Diab + ylim(0.05, 0.4) + xlim(55, 110) +
xlab("Diastolic Blood Pressure Reading") + theme(legend.position = "none") + ggtitle(" (a) Naive
Nondiabetic Patients - Diastolic")

# Plot the conditional Densities for Diabetics for Diastolic - Prescription
Hyp_Diastolic_Diabetes <- Hyp_Diastolic[Hyp_Diastolic$DIABETIC_DURING_VISIT == 1 &
Hyp_Diastolic$ON_EXISTING_HT_MEDICATION == 0,]
diastolic_plot_Diabetes <- ggplot(Hyp_Diastolic_Diabetes,
aes(Hyp_Diastolic_Diabetes$DIASTOLIC_VALUE, Hyp_Diastolic_Diabetes$PROBABILITY_OF_PRESCRIPTION,
color = factor(Hyp_Diastolic_Diabetes$SHOULD_BE_TREATED)))
diastolic_plot_Diabetes <- diastolic_plot_Diabetes + geom_point() + geom_vline(xintercept = 90,
linetype = "dashed", alpha = 0.6)
diastolic_plot_Diabetes <- diastolic_plot_Diabetes + ylab("Probability of Prescription")
diastolic_plot_Diabetes <- diastolic_plot_Diabetes + stat_smooth(method = "glm", method.args =
list(family = "gaussian", weights = as.vector(Hyp_Diastolic_Diabetes$N)), fullrange = FALSE,
alpha = 0.3) + stat_smooth(method = "glm", method.args = list(family = "gaussian"), fullrange =
TRUE, linetype = "dashed", lwd = 0.5, alpha = 0.15) + geom_point()
# diastolic_plot_Diabetes <- diastolic_plot_Diabetes + annotate("text", x = 75, y = 0.25, label =
lm_eqn(lm(Hyp_Diastolic_Diabetes$PROBABILITY~Hyp_Diastolic_Diabetes$DIASTOLIC_VALUE,
Hyp_Diastolic_Diabetes)), size = 3, parse=TRUE)
diastolic_plot_Diabetes <- diastolic_plot_Diabetes + ylim(0.1, 0.4) + xlim(55, 110) +
xlab("Diastolic Blood Pressure Reading") + theme(legend.position = "none") + ggtitle("(b) Naive
Diabetic Patients - Diastolic")

# Plot the conditional Densities for Systolic - Prescription
Hyp_Systolic_No_Diab <- Hyp_Systolic[Hyp_Systolic$DIABETIC_DURING_VISIT == 0 &
Hyp_Systolic$ON_EXISTING_HT_MEDICATION == 0,]
systolic_plot_No_Diab <- ggplot(Hyp_Systolic_No_Diab, aes(Hyp_Systolic_No_Diab$SYSTOLIC_VALUE,
Hyp_Systolic_No_Diab$PROBABILITY_OF_PRESCRIPTION, color =
factor(Hyp_Systolic_No_Diab$SHOULD_BE_TREATED)))
systolic_plot_No_Diab <- systolic_plot_No_Diab + geom_point() + geom_vline(xintercept = c(140),
linetype = "dashed", alpha = 0.6)
systolic_plot_No_Diab <- systolic_plot_No_Diab + ylab("Probability of Prescription")
systolic_plot_No_Diab <- systolic_plot_No_Diab + stat_smooth(method = "glm", method.args =
list(family = "gaussian"), fullrange = FALSE, alpha = 0.4) + stat_smooth(method = "glm",
method.args = list(family = "gaussian"), fullrange = TRUE, linetype = "dashed", lwd = 0.5, alpha
= 0.15) + geom_point()
systolic_plot_No_Diab <- systolic_plot_No_Diab + ylim(0.05, 0.25) + xlim(110,160) +
xlab("Systolic Blood Pressure Reading") + theme(legend.position = "none") + ggtitle("(c) Naive
Nondiabetic Patients - Systolic")

# Plot the conditional Densities for Diabetics for Systolic - Prescription
Hyp_Systolic_Diab <- Hyp_Systolic[Hyp_Systolic$DIABETIC_DURING_VISIT == 1 &
Hyp_Systolic$ON_EXISTING_HT_MEDICATION == 0,]
systolic_plot_Diab <- ggplot(Hyp_Systolic_Diab, aes(Hyp_Systolic_Diab$SYSTOLIC_VALUE,
Hyp_Systolic_Diab$PROBABILITY_OF_PRESCRIPTION, color =
factor(Hyp_Systolic_Diab$SHOULD_BE_TREATED)))
systolic_plot_Diab <- systolic_plot_Diab + geom_point() + geom_vline(xintercept = c(130),
linetype = "dashed", alpha = 0.6)
systolic_plot_Diab <- systolic_plot_Diab + ylab("Probability of Prescription")
systolic_plot_Diab <- systolic_plot_Diab + stat_smooth(method = "glm", method.args = list(family
= "gaussian"), fullrange = FALSE, alpha = 0.4) + stat_smooth(method = "glm", method.args =
```

```
list(family = "gaussian"), fullrange = TRUE, linetype = "dashed", lwd = 0.5, alpha = 0.15) +
geom_point()
systolic_plot_Diab <- systolic_plot_Diab + ylim(0.10, 0.4) + xlim(110, 160) + xlab("Systolic
Blood Pressure Reading") + theme(legend.position = "none") + ggtitle("(d) Naive Diabetic Patients
- Systolic")

multiplot(systolic_plot_No_Diab, systolic_plot_Diab, diastolic_plot_No_Diab,
diastolic_plot_Diabetes,  cols = 2)
#########################################################################
### Histograms of density, with Normal distribution overlays
### Shown for Systolic and Diastolic
###
#########################################################################
# Diastolic
gg_d_density <- ggplot(Hyp, aes(x=Hyp$DIASTOLIC_VALUE)) + geom_histogram(color = "black", fill =
"white", aes(y = ..density..), bins = (((max(Hyp$DIASTOLIC_VALUE)) -
(min(Hyp$DIASTOLIC_VALUE)))/2+1))
gg_d_density <- gg_d_density + scale_x_continuous(breaks = round(seq(min(Hyp$DIASTOLIC_VALUE)-1,
max(Hyp$DIASTOLIC_VALUE), by = 5),1)) + ylab("Probability")
gg_d_density <- gg_d_density + theme(text = element_text(size=20))
gg_d_density <- gg_d_density + xlab("Diastolic Blood Pressure Reading") + geom_vline(xintercept =
90, linetype = "dashed", color = "dark green", size = 1)
gg_d_density <- gg_d_density + stat_function(fun=dnorm, args=list(mean=mean(Hyp$DIASTOLIC_VALUE),
sd=sd(Hyp$DIASTOLIC_VALUE)), color = "red", size = 1, linetype = "dashed", aes(color = "Normal
Dist."))
gg_d_density

# Plot distribution by race - diastolic
facet_diastolic <- ggplot(Hyp, aes(x=Hyp$DIASTOLIC_VALUE)) + geom_histogram(color = "black", fill
= "white", aes(y = ..density..), bins = (((max(Hyp$DIASTOLIC_VALUE)) -
(min(Hyp$DIASTOLIC_VALUE)))/2+1))
facet_diastolic <- facet_diastolic + facet_wrap(~PATIENT_RACE_CODE)
facet_diastolic <- facet_diastolic + xlab("Diastolic Blood Pressure Reading") +
geom_vline(xintercept = 90, linetype = "dashed", color = "dark green")
facet_diastolic + ylim(0, 0.1)

# Systolic
gg_s_density <- ggplot(Hyp, aes(x=Hyp$SYSTOLIC_VALUE)) + geom_histogram(color = "black", fill =
"white", aes(y = ..density..), bins = (((max(Hyp$SYSTOLIC_VALUE)) -
(min(Hyp$SYSTOLIC_VALUE)))/2+1))
gg_s_density <- gg_s_density + scale_x_continuous(breaks = round(seq(min(Hyp$SYSTOLIC_VALUE)-1,
max(Hyp$SYSTOLIC_VALUE), by = 5),1)) + ylab("Probability")
gg_s_density <- gg_s_density + theme(text = element_text(size=20))
gg_s_density <- gg_s_density + xlab("Systolic Blood Pressure Reading") + geom_vline(xintercept =
140, linetype = "dashed", color = "dark green")
gg_s_density + stat_function(fun=dnorm, args=list(mean=mean(Hyp$SYSTOLIC_VALUE),
sd=sd(Hyp$SYSTOLIC_VALUE)), color = "red", linetype = "dashed", aes(color = "Normal Dist."))

# Plot distribution by race - systolic
facet_systolic <- ggplot(Hyp, aes(x=Hyp$SYSTOLIC_VALUE)) + geom_histogram(color = "black", fill =
"white", aes(y = ..density..), bins = (((max(Hyp$SYSTOLIC_VALUE)) -
(min(Hyp$SYSTOLIC_VALUE)))/2+1))
facet_systolic <- facet_systolic + facet_grid(. ~ PATIENT_RACE_CODE)
facet_systolic <- facet_systolic + xlab("Systolic Blood Pressure Reading") +
geom_vline(xintercept = 140, linetype = "dashed", color = "dark green")
facet_systolic + ylim(0, 0.1)

multiplot(gg_d_density, gg_s_density, cols = 1)
# PDF of density by BP reading - placeholder in case useful.
plot(density(Hyp$SYSTOLIC_VALUE))
curve(dnorm(x, mean=mean(Hyp$SYSTOLIC_VALUE), sd=sd(Hyp$SYSTOLIC)), col="darkblue", lwd=2,
add=TRUE, yaxt="n")

# Using data from the entire dataset, plot the surface showing treatment                  #
# probabilities for each systolic reading, conditional on a specific diastolic reading    #
p <- ggplot(Hyp_Systolic_Diastolic[Hyp_Systolic_Diastolic$DIASTOLIC_VALUE>86 &
Hyp_Systolic_Diastolic$DIASTOLIC_VALUE<89 & Hyp_Systolic_Diastolic$DIABETIC_DURING_VISIT == 0 &
Hyp_Systolic_Diastolic$ON_EXISTING_HT_MEDICATION == 0,], aes(SYSTOLIC_VALUE,
PROBABILITY_OF_PRESCRIPTION, color = factor(N_DIASTOLIC))) + geom_point(size = 0.06) +
geom_vline(xintercept = 140, linetype = "dashed", color = "dark green")
p + facet_wrap(~DIASTOLIC_VALUE, ncol = 4) + theme(strip.text = element_text(size=8)) +
theme(legend.position="none") + theme(axis.text = element_text(size = 8)) +
scale_y_continuous(limits = c(0, 0.4))
```

```
p <- ggplot(Hyp_Systolic_Diastolic[Hyp_Systolic_Diastolic$SYSTOLIC_VALUE %in% seq(111, 169, by =
2),], aes(DIASTOLIC_VALUE, PROBABILITY_OF_PRESCRIPTION, color = factor(N))) + geom_point(size =
0.08) + geom_vline(xintercept = 90, linetype = "dashed", color = "dark green")
p + facet_wrap(~SYSTOLIC_VALUE, ncol = 10) + theme(strip.text = element_text(size=8)) +
theme(legend.position="none") + theme(axis.text = element_text(size = 8)) +
scale_y_continuous(limits = c(0, 0.4))
```