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Population-based Testing and Treatment Characteristics for Chronic Myelogenous Leukemia

Timothy Styles, MD, MPH[a], **Manxia Wu, MD, MPH**[a], **Reda Wilson, MPH, CTR**[a], **Frances Babcock, CTR**[a], **David Butterworth**[a], **Dee W. West, Ph.D.**[b], and **Lisa C. Richardson, MD, MPH**[a]

[a]Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

[b]Cancer Registry of Greater California, Public Health Institute, Sacramento, California and Stanford University School of Medicine, Palo Alto, California

Abstract

Introduction—National and International Hematology/Oncology Practice Guidelines recommend testing for the BCR-ABL mutation for definitive diagnosis of chronic myeloid leukemia (CML) to allow for appropriate treatment with a Tyrosine Kinase Inhibitor (TKI). The purpose of our study was to describe population-based testing and treatment practice characteristics for patients diagnosed with CML.

Methods—We analyzed cases of CML using 2011 data from 10 state registries which are part of the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries. We describe completeness of testing for the BCR-ABL gene and availability of outpatient treatment with TKIs and associated characteristics.

Results—A total of 685 cases of CML were identified; 55% (374) had a documented BCR-ABL gene test with 96% (360) of these being positive for the BCR-ABL gene and the remaining 4% (14) either testing negative or had a missing result. Registries were able to identify the use of TKIs in 54% (369) of patients, though only 43% (296) had a corresponding BCR-ABL gene test documented. One state registry reported a significantly lower percentage of patients being tested for the BCR-ABL gene (25%) and receiving TKI treatment (21%). Limiting analysis to CML case reports from the remaining nine CER registries, 78% (305) patients had a documented BCR-ABL gene test and 79% (308) had documented treatment with a TKI. Receipt of testing or treatment for these nine states did not vary by sex, race, ethnicity, census tract poverty level, census tract urbanization, or insurance status; BCR-ABL testing varied by state of residence and BCR-ABL testing and TKI therapy occurred less often with increasing age (OR: 0.97, 95%CI: 0.95–0.99; OR: 0.97, 95%CI: 0.96–0.99 respectively).

Address correspondence to: Tim Styles, MD, MPH, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333. vii6@cdc.gov.

The findings and conclusions are those of the authors and do not necessarily represent the official position of their affiliations or the Centers for Disease Control and Prevention.

Conclusions—Collection of detailed CML data vary significantly by states. A majority of the case patients had appropriate testing for the BCR-ABL gene and treatment with tyrosine kinase inhibitors. However, BCR-ABL testing and TKI treatment decreased with increasing age. Further research is needed to understand CML coding, testing, and treatment disparities.

Keywords

Chronic Myelogenous (Myeloid) Leukemia; Comparative Effectiveness Research; population-based registry; National Program of Cancer Registries; NPCR; targeted therapy; BCR-ABL mutation

Introduction

Chronic Myeloid Leukemia (CML) is a neoplasm resulting from uncontrolled growth of bone marrow stem cells of the myeloid cell line. Most people found to have an elevated neutrophil count will not have CML. Even though a presumptive diagnosis can be made based on clinical features and routine blood work, a definitive diagnosis of CML requires either the demonstration of the t(9;22) Philadelphia chromosome translocation (by fluorescent in situ hybridization or FISH), or *BCR-ABL1* fusion gene (qRT-PCR).[1, 2] The BCR-ABL gene is a result of a chromosomal translocation between Chromosome 9 and 22 resulting in an overproduction of a tyrosine kinase protein ultimately leading to uncontrolled cell proliferation and lack of normal cell death. Tyrosine Kinase Inhibitors, or TKIs, bind to the active site of the BCR-ABL protein (a tyrosine kinase) stopping cell growth and leading to apoptosis (natural cell death). Verifying the presence of the Philadelphia Chromosome became even more important with the advent of TKIs that target the abnormal kinase proteins. Imatinib (Gleevec) was the first TKI developed in the late 1990s and first approved by the FDA for first line use for CML in 2002.[3] By 2009, national and international hematology practice guidelines clearly recommended both BCR-ABL gene testing for accurate diagnosis of CML and prompt treatment with a tyrosine kinase inhibitor such as Imatinib, Dasatinib (Srpycel), or Nilotinib (Tasigna).[4, 5, 6] However, population-based evaluation of BCR-ABL testing and treatments received by CML patients is still limited.

The goals of our study included assessing the ability of state registries to collect treatment data from a variety medical care settings, including non-hospital outpatient settings; provide a population-based, real-world look at testing and treatment practices outside of randomized clinical trials (RCT); and evaluate patient characteristics that may affect BCR-ABL gene testing and TKI therapy, such as demographic, socioeconomic status (SES), and clinical features such as comorbidities.

Methods

To capture unique population level testing and treatment data, the Centers for Disease Control and Prevention's (CDC's), National Program of Cancer Registries (NPCR) applied for and was granted federal funding to Enhance Cancer Registry Data for Comparative Effectiveness Research (CER).[7] Comparative effectiveness research provides information for practitioners and patients alike either by describing benefits and harms of different treatment options and strategies currently available, or by performing new studies to evaluate

effectiveness of treatment in “real world” settings.[8] Eight state cancer registries (Alaska, Colorado, Idaho, Louisiana, North Carolina, New Hampshire, Rhode Island, Texas) and metropolitan centers in two states (Sacramento Area in California and the Miami-Dade, Orlando, and Tampa areas in Florida) were selected through a competitive process, as Specialized Registries for the collection of CER. This NPCR CER population represents approximately 27% of the United States population and were chosen to ensure racial/ethnic diversity. The National Program of Cancer Registries Cancer Surveillance System was granted approval for collection of CER data from CDC’s Institutional Review Board (IRB) and from the Office of Management and Budget as collection of additional data items and submission of de-identified information were authorized by existing cancer reporting laws and regulations in participating states. Individual states also received state level IRB approval or were considered exempt as the collection of enhanced registry data was considered public health surveillance. All additional data items were collected through re-abstraction of the patient medical record or direct data linkages with medical care facilities; no patients were contacted for this project.

CER specific data, including detailed testing and treatment information, were collected from medical care providers for all CML diagnoses in 2011, as well as for cancers of the colon, rectum, and breast. Registries built upon routine NAACCR abstracts adding CER specific data typically through one of three methods: (1) onsite visits to hospital, hospital based and non-hospital hematology/oncology practice groups and private practice physician offices, (2) obtained hard copies or secured remote access from these facilities, (3) or direct transmission of data by the facility. A detailed description of NPCR’s CER methods and additional data elements collected has been previously described.[9] Our study includes all patients diagnosed with either BCR-ABL+ CML (International Classification of Disease (ICD)-O3 Histology code 9875) and CML NOS (ICD-O3 Histology code 9863) a code generally used as a provisional diagnosis when a myelogenous leukemia is identified prior to genetic studies being completed.[10] Type of BCR-ABL gene test was collected, including cytogenetic testing, fluorescence in situ hybridization (FISH), qualitative reverse transcriptase polymerase chain reaction (RT-PCR), and quantitative RT-PCR. Date the test was performed and results were recorded; if no date was found, a date flag was required to indicate the reason (not found, not performed, etc.). Through a combination of testing results, dates, and date flags we grouped patients into four categories: 1) BCR-ABL gene test performed, with positive result; 2) BCR-ABL gene not tested or not applicable; 3) unknown if BCR-ABL gene testing occurred; and 4)BCR-ABL gene test performed, either no result recorded or negative result. No information was collected to understand when genetic testing was deemed not applicable or not performed. Coding options were not sensitive enough to differentiate between those tested with no result recorded or a negative result.

The project collected up to six first course chemotherapy agents for each patient using the standardized National Cancer Institute numeric identifier, or NSC number, created when a medication is undergoing therapeutic development testing. Registrars could also record whether there was indication in the medical record of “Chemotherapy not planned” or “Unknown if chemotherapy planned or not required”. Additional standard NPCR variables such as RxDateChemo (date of initiation of chemotherapy) collected from hospitals with a

Commission on Cancer Approved Cancer Program (CoC) were also cross-referenced to CER specific chemotherapy fields. A patient was categorized as receiving a tyrosine kinase inhibitor if one of the agents recorded as part of first course therapy included Imatinib, Disatinib, or Nilotinib.

Insurance status at time of diagnosis was collected and additional socio-economic status (SES) measures, including census tract poverty and urbanization, were based on a patient's address at time of diagnosis. Insurance status was grouped into categories of no insurance, private insurance (includes Medicare with private supplement), Medicare, Medicaid/Other Public (Veterans Affairs, Tricare, Indian Health Service), insurance not otherwise specified, and unknown/missing insurance. Census tract poverty and urbanization were determined based on census tract associated with patient address at time of diagnosis and SES measure cut offs were selected to be consistent with current literature.[11, 12] Impoverished communities were selected as those where over 20% of the population in the census tract fell below the poverty line.[13] Census tract urbanization was defined as urban if all areas in the census tract were considered in an urban setting, rural if all areas in the census tract were considered in a rural setting, and mixed if a combination of rural and urban areas in a census tract.[14]

Attempts were also made to collect patient level characteristics, such as tobacco use and comorbid conditions, which were obtained through medical records and through state registry linkages with hospital discharge files and other data sets. We combined available information on patients' history of smoking cigarettes, use of other smoking tobacco (pipes, etc.), chewing tobacco, and other tobacco into one variable to indicate current tobacco use, former tobacco use (quit for more than one year), no tobacco use, and unknown tobacco use history. Comorbidities were re-abstracted using ICD-9 coding and were placed into one of three categories for later analysis: 1) comorbidity based on the Charlson comorbidity scale indicating more severe comorbidity that may affect treatment options (e.g. history of cardiac or hepatic disease), 2) Non-Charlson comorbidity considered less severe in nature, 3) no comorbidity / unknown as these two codes could not be differentiated.[15, 16]

Analyses were conducted using the enhanced CER dataset with updated vital status as submitted by the 10 Specialized Registry sites to the NPCR Cancer Surveillance System in November 2014. We used SAS version 9.3 (SAS Institute, Cary, NC) to perform a descriptive analysis assessing factors associated with BCR-ABL gene testing and TKI treatment for CML patients. Bivariate analysis was performed using Pearson's Chi Square and multi-variable analysis was completed using multi-variable logistic regression analysis. Models were developed for the dependent variable BCR-ABL testing (whether a test was recorded or not) and a Tyrosine Kinase Inhibitor (recorded or not recorded) in the patient record.

Results

Of 805 CML cases in the NPCR CER dataset, we excluded 92 cases reported after the completion of the project, nine autopsy only cases, one case of unknown age, three CML NOS cases that died within an unknown time from diagnosis and 15 that died within the first

seven days of diagnosis. This window of seven days was selected since BCR-ABL gene testing can range from 3–7 days, a necessity for definitive diagnosis and to confirm candidacy for TKI therapy. Our final sample contains 685 cases of CML. Of them, 51% (352) were recorded as having BCR-ABL positive CML; the remaining 49% (333) were recorded as CML NOS.

Patient demographic information is displayed in Table 1. A slight majority of patients diagnosed with CML were males (55% [376]). Median age was 58 years with a range from 5–99 years. Race/ethnicity data were available for 677 patients of which 64% (440) were Non-Hispanic White, 14% (97) Non-Hispanic Black, 2% (14) Non-Hispanic Other, and 18% (126) Hispanic all races. Primary payer information at diagnosis showed a majority (91% [626]) had documentation of medical insurance; 41% (282) had private insurance, 5% (32) had insurance not otherwise specified, 13% (90) Medicaid or other government sponsored (Tricare/Military, Veterans Affairs, Indian Health Service), 23% (154) Medicare, 10% (68) were uninsured at diagnosis, and the remaining 9% (59) had unknown/missing insurance status. The majority of patients (57% [391]) lived in urban areas as defined by the US Census Bureau, with most of the remaining living in census tracts where the population lived in a mixed urban or rural setting (34% [235]) or purely rural census tracts (8% [55]); four were missing census tract data. Eighty-one percent (555) of patients lived in census tracts where less than 20% of the families in the census tract had income below the poverty line in the last 12 months. Distribution of diagnoses in the 10 CER sites are presented in Table 1. Nearly half of the cases came from State A (43% [292]) with States B-E contributing the bulk of the remaining cases (46% [313]), although age-adjusted incidence rates in these states based on 2010 population were similar ranging between 1.6–2.2 per 100,000.[17]

Patient characteristics, including tobacco use and comorbidities, can affect the risk of developing CML and/or the ability to receive various types of treatment including TKIs.[18, 19] Data collected from medical documentation showed forty percent (273) of patients reported never using any type of tobacco product, 17% (119) were former tobacco users, and only 10% (66) were current users. One third (227) had an unknown tobacco history, the information was not stated in the record, not collected, or missing. Of those with comorbid conditions collected, 34% (232) were non-Charlson comorbidities and 23% (154) were Charlson comorbidities; the remaining 44% (299) had a non-specific code indicating the patient had no comorbidities, the information was not known, not collected, or comorbidity data was missing in the chart.

Of the 685 patients diagnosed with CML, 55% (374) had a documented BCR-ABL gene test recorded by the cancer registry, with 96% (360) of these being positive for the BCR-ABL gene. The other 4% (14) of those tested were either negative or the test was ordered but no result was recorded. Of the 45% (311) without a test recorded, most (98% [305]) had a flag to indicate the test was not done or the test was not applicable; the remaining 2% (6) had unknown testing status.

We performed bivariate and multivariable logistic regression analysis to evaluate potential factors associated with having a BCR-ABL test ordered (Table 2). As results were similar we will only present multivariable logistic regression analysis here (see Table 2 for bivariate

results). On initial analysis, one factor, state of residence at diagnosis, stood out as the strongest predictor of receiving a BCR-ABL gene test. One state, State A, had significantly fewer cases being reported as having had the BCR-ABL gene test compared to the other states (24% tested in State A compared to 72% of all the other states combined; range of individual states 24%–96%). Discussion with State A cancer registry revealed data collection was too resource intensive for staff at the time; therefore state A was removed from bivariate and multivariable logistic regression analysis. In addition, tobacco use and comorbidity were also excluded because of a high percent of uninterpretable data (33% and 44% respectfully). Multivariable models included age (as a continuous variable), sex, race/ethnicity, insurance at diagnosis, census tract poverty and urbanization, and state at diagnosis. Age and state of residence remained the only significant factors associated with BCR-ABL gene testing in our logistic regression model. Likelihood of BCR-ABL decreased with increasing age (OR: 0.97, 95%CI: 0.95–0.99) and residents of states C, D, and E were more likely to have BCR-ABL testing compared to state B (state C OR: 20.94, 95%CI: 4.69–93.51; state D OR: 3.19, 95%CI: 1.16–8.74; state E OR: 3.22, 95%CI: 1.18–8.76).

Tyrosine Kinase Inhibitors use was recorded for 54% (369) of patients (Table 3a); 296 of whom also had documented BCR-ABL gene testing. Of the 46% (316) patients not receiving TKIs, 77 received other chemotherapy agents (primarily Hydroxyurea) and 239 were recoded as no planned chemotherapy (102), unknown if chemotherapy was planned (29), or were left blank (108) (data not shown). However, state A reported similar difficulties capturing TKI data due to limited resources. Removing State A (Table 3b), resulted in nearly 78% (305) of the 393 CML patients from states B-J with documented treatment with a TKI. The remaining 22% (88) received other chemotherapy (33), no chemotherapy planned (35), unknown if received chemotherapy (8), or was left blank (8). We performed bivariate and multivariable logistic regression analysis to evaluate factors associated with a patient receiving a TKI as part of their first course therapy (Table 4). We again removed the variables for comorbidity and tobacco use as well as the data from state A due to missing or uninterpretable data. In addition to significant fewer patients being recorded as having received a TKI in state A, chemotherapy data was missing all-together in 27% (80) of state A CML case reports despite most having a valid date of chemotherapy completed by CoC hospitals [RxDateChemo]. State A was also responsible for 66% of those coded as “Chemotherapy not planned” and 72% of those coded as “Unknown if chemotherapy planned or Not required”. We included age, sex, race/ethnicity, insurance at diagnosis, census tract poverty and urbanization, and state at diagnosis in the multivariable logistic regression model. Age was used as a continuous variable and remained significantly associated (borderline) with receipt of TKI therapy (OR: 0.97, 95%CI: 0.96–0.99).

Discussion

National and international guidelines, including the National Comprehensive Cancer Network (NCCN), recommend testing for the BCR-ABL gene to make a definitive diagnosis of CML allowing for prompt treatment with a TKI.[4, 5, 6] This study attempted to capture population based BCR-ABL gene testing for CML patients and guideline therapy with a tyrosine kinase inhibitor. Our results show the majority (55%) of patients diagnosed with CML were tested by one of four means of genetic testing. However, collected data on testing

and treatment varied significantly by state of diagnosis. Based on having a higher percentage of missing information, one state appeared to have had a more difficult time collecting information on CML diagnosis and treatment. This could be due to less supportive legal authority for public health surveillance data collection activities, or may indicate more limited health record access or incomplete testing data present in the medical record. States also differed by geographic area; total population; number of CoC hospitals; and personnel resources, all affecting workload by the associated state registry.

Another possibility was that patients were not being tested appropriately for the BCR-ABL gene, resulting in fewer cases eligible for TKI therapy and inaccurate annual rates of CML reported. As noted, our study did show nearly 50% of CML cases were diagnosed with CML NOS, a diagnosis that should only be used as a temporary placeholder until a definitive diagnosis is determined. A recent study by Mertz et.al. also showed high use of CML NOS with over 80% of reported CML cases having this diagnosis.[20] As a comparison, Höglund et.al. evaluated 779 CML cases from 2002–2009 in Sweden and all but 24 had readily available BCR-ABL gene testing results through their national registry (would result in a 3% use of CML NOS). Also noted by Höglund, Swedish annual rates of CML were lower at 1.0 case per 100,000 annually compared to SEER 18 annual incidence reports from 2006–2010 at 1.6 cases per 100,000 per year.[21] States included in the NPCR CER study have an annual age adjusted rate per 100,000 of 1.8 per year between 2006–2011.[17] Inaccurate coding or diagnosis, possibly due to incomplete gene testing information, is one possible explanation for the rate differences between our countries. This is plausible as cancer registrars may need additional training on hematopoietic cancers, especially training related to gene testing. However, rate differences between these studies may represent different numerators. For example, rates calculated by Höglund included only BCR-ABL+ CML and CML NOS cases, but the SEER 18 rates as well as the NPCR- SEER combined U.S. Cancer Statistics (USCS) rates are calculated using a CML recode variable that includes not only CML NOS and BCR-ABL+ CML cases but also atypical CML (aCML), Chronic Myelomonocytic Leukemia (CMML), and Juvenile Myelomonocytic Leukemia (JMML) cases. In their analysis of all-cause mortality of patients diagnosed with CML, Brunner et.al. recognized that CML cases included in the recode are not all eligible for TKI therapy and would have differing overall survival expectation, thus limiting their analysis to BCR-ABL+ CML and CML NOS.[22] Recalculating rates of CML in CER states using only, CML NOS and BCR-ABL+ CML results in a decrease to 1.3 per 100,000. Overall national incidence rates for that same time period using USCS data were 1.2 per 100,000 per year with 71% coded as CML NOS. Although the national rate more closely resembles findings in Europe when limiting diagnoses to CML NOS and BCR-ABL+ CML, our high use of CML NOS may include non-CML cases classified as such before definitive diagnostic studies were completed.[23]

Although our CER data are only a snapshot of one diagnosis year, the data showed that a slight majority of patients (54%) received a tyrosine kinase inhibitor as part of their first course therapy. This percent increases to 78% of patients if data from State A is removed from the analysis (State A reported only 21% recorded TKI use). This is similar to what was seen in Höglund's study where it was reported that approximately 85% of CML cases in Sweden in 2009 were treated with TKIs within the first year after diagnosis.[21] Also

consistent with the Swedish study, age was a significant predictor of receiving treatment with a TKI as younger patients were more likely to be treated with TKIs than older patients.

Strengths

This study is a multi-state population-based analysis of BCR-ABL testing and treatment for CML representing nearly 27% of the United States. Data collected for the NPCR CER study included previously uncaptured chemotherapy treatment detail including outpatient medications. This study demonstrates complex outpatient diagnostic testing and outpatient treatment data can be captured by state registries. However, we have also shown that collection of these data can vary significantly between states and is likely multi-factorial. The CDC Specialized Registries in this study had not previously collected this level of detailed testing and treatment data. It is important to learn from their efforts and continue to refine methods of collecting population-based cancer data appropriate for comparative effectiveness research and patient centered outcomes research to better describe testing and treatments received by patients outside of a clinical trial. Taking advantage of Meaningful Use and other Electronic Medical Record utilization to make collecting this type of data more economical on a large scale will be important going forward.

Limitations

State and regional cancer registries participating in the NPCR CER project were selected in part because of their demographic make-up allowing for a representative sample of the US population. However, incomplete data and questionable quality in one state resulted in the need to exclude that state from analyses thereby limiting generalizability of our findings. We were unable to assess the differences in available testing and treatment data or what factors aided the ability of a specific state registry to collect CER data. Possible ways to do this in the future would be to review source data, including text fields, for accuracy of data coding. Source data may have additional information that would have allowed for the evaluation of discordant pairs. These included receiving TKI therapy despite having no BCR-ABL gene test performed (Table 3) or not receiving TKI therapy despite having a recorded BCR-ABL+ gene test, thus, a candidate for TKIs per guideline recommendation. Additional discrepancies were found in diagnostic codes used with those being diagnosed with CML NOS despite having a positive BCR-ABL gene test (7%[49]), or being diagnosed with BCR-ABL + CML despite having the record indicate that the gene testing was not performed or not applicable (6%[41], data not shown). Another limitation is our inability to assess the phase of disease for individual patients, i.e. chronic, acute, or Blast Crisis. This would change treatment options and may place patients on non-TKI medications. However, if a patient was not in a clinical trial, treatment should still include a TKI and therefore this was a minor limitation.[4] Finally the large number of unknown/missing tobacco and comorbidity data made it difficult to assess possible health risk factors and health conditions that increase the risk of developing CML such as smoking history, or limit TKI use such as those with hepatic impairment or congestive heart failure. The NPCR CER Specialized Registries reported that tobacco and comorbidity information was not always in the medical record or not readily apparent.

Conclusion

We have shown that collecting detailed testing and treatment information from medical records is possible by state cancer registries. In states capable of collecting detailed CML data we found a majority of patients had documented BCR-ABL gene testing for definitive diagnosis, thus, making them candidates for Tyrosine Kinase Inhibitors. Correspondingly, we found a slight majority of patients received guideline concordant care with a TKI. It is important to continue efforts to collect population based comparative effectiveness research to better describe testing and treatments received by patients outside of a clinical trial. Usefulness of data could be improved through complete documentation of test results and through careful examination of coding practices to ensure proper diagnosis of CML. Additionally, collecting intermediate and long term outcomes at the population level will add to our understanding of the efficacy of various therapies. However, we do need further research to understand availability of data in different states as well as the need for additional training in identifying and coding hematopoietic cancers. The appropriateness of separating non-CML leukemias—such as aCML, CMML, and JMML— and CML leukemias in national coding schemes needs to be evaluated given the differences in treatments and overall survival so that CML statistics can be accurately reported.

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Table 1

Demographic Characteristics for CML Cases Identified as Part of the NPCR CER Dataset, 2011.

	N	%
Total CML Cases (BCR-ABL+ CML and CML NOS)	685	100.0%
Sex		
Male	376	54.9%
Female	308	45.0%
Other (transsexual)	1	0.1%
Age at Diagnosis		
<50	237	34.6%
50–59	125	18.2%
60–69	129	18.8%
≥70	194	28.3%
Race/Ethnicity		
Non-Hispanic White	440	64.2%
Non-Hispanic Black	97	14.2%
Non-Hispanic Other-(AI/AN/AIPI)	14	2.0%
Hispanic (all races)	126	18.4%
Other unspecified/Unknown/Missing	8	1.2%
Health Insurance		
Private	282	41.2%
Insurance NOS	32	4.7%
Medicaid and other public insurance	90	13.1%
Medicare	154	22.5%
No Insurance	68	9.9%
Unknown/Missing/Blank	59	8.6%
Census Tract Urbanization *		
100% Urban	391	57.1%
100% Rural	55	8.0%
Mixed Urban/Rural	235	34.3%
Missing	4	0.6%
Census Tract Poverty **		
Poverty <20%	555	81.0%
Poverty ≥20%	126	18.4%
Blank/Missing	4	0.6%
Tobacco		
Never Used Tobacco Products	273	39.9%
Current user of Tobacco Products	66	9.6%
Former user of Tobacco Products	119	17.4%
Unknown / Missing / Not collected	227	33.1%
Comorbidity		
No Comorbidity / Unknown / Missing / Not collected	299	43.6%

	N	%
At least one NON-Charlson comorbidity	232	33.9%
At least one Charlson comorbidity	154	22.5%
State of Residence		
State A	292	42.6%
State B	120	17.5%
State C	73	10.7%
State D	64	9.3%
State E	56	8.2%
State F	29	4.2%
State G	20	2.9%
State H	15	2.2%
State I	10	1.5%
State J	6	0.9%

* Census tracts urbanization defined as urban if 100% of addresses in the census tract are located in an urban setting, 100% rural if 100% of addresses in the census tract are located in an urban setting, or mixed

** Poverty- patient categorized into two categories based on census tract of residence (i.e. where less than 20% of the families in the census tract had income below the poverty line in the last 12 months OR 20% or more of households in patient census tract had income below the poverty line in the last 12 months)

Table 2

BCR-ABL genetic testing descriptive, bivariate, and multi-variable analysis

Variables	CML cases with documented BCR-ABL gene testing (excluding State A) N=393 n= (%*)	Bivariate Analysis (excluding State A) OR (95% CI)	Multivariable Analysis (excluding State A) OR (95% CI)
Age at Diagnosis			
<50	116 (84.7%)	ref	
50–59	62 (80.5%)	0.748 (0.360–1.554)	
60–69	56 (75.7%)	0.563 (0.278–1.141)	
70–79	71 (67.6%)	**0.378 (0.204–0.702)**	
Age as Continuous			**0.971 (0.953–0.990)**
Sex			
Male	161 (78.9%)	ref	ref
Female	144 (76.6%)	0.874 (0.543–1.408)	0.873 (0.496–1.539
Race/Ethnicity			
Non-Hispanic White	201 (75.6%)	ref	ref
Non-Hispanic Black	47 (81.0%)	1.382 (0.677–2.820)	1.054 (0.443–2.510)
Hispanic	44 (81.5%)	1.423 (0.678–2.986)	1.296 (0.516–3.255)
Non-Hispanic Other	7 (77.8%)	1.132 (0.229–5.585)	1.456 (0.214–9.900)
Missing	6		
Health Insurance			
Private	148 (82.2%)	ref	ref
Insurance NOS	15 (71.4%)	0.540 (0.195–1.500)	0.310 (0.096–1.004)
Medicaid and other public insurance	51 (78.5%)	0.788 (0.390–1.593)	0.587 (0.259–1.332)
Medicare	59 (72.8%)	0.580 (0.312–1.079)	0.682 (0.315–1.481)
No Insurance	21 (80.8%)	0.908 (0.319–2.589)	0.566 (0.171–1.876)
Missing	20		
Census Tract Residence **			
100% Urban	162 (76.8%)	ref	ref
100% Rural	25 (78.1%)	1.080 (0.441–2.649)	1.253 (0.409–3.838)
Mixed	114 (78.1%)	1.078 (0.650–1.787)	1.832 (0.904–3.713)
Missing	4		
Census Track Poverty ***			
Poverty <20%	251 (75.8%)	ref	ref
Poverty ≥ 20%	50 (86.2%)	1.992 (0.906–4.379)	1.937 (0.788–4.758)
Missing	4		
State of Residence			
State A **[69 (23.6%) BCR-ABL tested]**			
State B	81 (67.5%)	ref	ref

Variables	CML cases with documented BCR-ABL gene testing (excluding State A) N=393 n= (%*)	Bivariate Analysis (excluding State A) OR (95% CI)	Multivariable Analysis (excluding State A) OR (95% CI)
State C	70 (95.9%)	**11.231 (3.326–37.925)**	**20.944 (4.694–93.510)**
State D	53 (82.8%)	**2.320 (1.092–4.928)**	**3.189 (1.163–8.742)**
State E	46 (82.1%)	**2.215 (1.012–4.848)**	**3.215 (1.180–8.760)**
State F	15 (51.7%)	0.516 (0.227–1.174)	0.644 (0.237–1.749)
State G	17 (85.0%)	2.728 (0.754–9.867)	3.454 (0.885–13.485)
State H	11 (73.3%)	1.324 (0.396–4.425)	1.539 (0.368–6.433)
State I	9 (90.0%)	4.333 (0.530–35.422)	>999.999 (<0.001–>999.999)
State J	3 (50.0%)	0.481 (0.093–2.495)	0.088 (0.006–1.393)

*% of category tested for BCR-ABL gene

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***Poverty- patient categorized into two categories based on census tract of residence (i.e. where less than 20% of the families in the census tract had income below the poverty line in the last 12 months OR 20% or more of households in patient census tract had income below the poverty line in the last 12 months)

Note: **Bolding** indicates significant finding

Table 3

Tyrosine Kinase Inhibitor use by BCR_ABL Test result

a: State A included

	Receipt of TKIs (N=685)		
BCR_ABL Testing	**TKI given**	**No TKI given**	**Total**
Tested (360 positive)	**296 (43.2%)**	78 (11.4%)	374 (54.9%)
Not Tested or Unknown	73 (10.7%)	**238 (34.7%)**	311 (45.4%)
Total	369 (53.9%)	316 (6.7%)	685

b: State A removed

	Receipt of TKIs (n=393)		
BCR_ABL Testing	**TKI given**	**No TKI given**	**Total**
Tested (360 positive)	**267 (67.9%)**	41 (10.4%)	308 (78.4%)
Not Tested or Unknown	38 (9.7%)	**47 (12.0%)**	85 (21.6%)
Total	305 (77.6%)	88 (22.4%)	393

Table 4

TKI therapy, descriptives, bivariate analysis, and multivariable analysis

Variables	CML cases with documented TKI therapy (excluding state A) N=393 n (%*)	Bivariate Analysis (excluding State A) OR (95% CI)	Multivariable Analysis (excluding State A) OR (95% CI)
Age at Diagnosis			
<50	115 (83.9%)	ref	
50–59	64 (83.1%)	0.942 (0.445–1.995)	
60–69	59 (79.7%)	0.752 (0.364–1.557)	
70–79	70 (66.7%)	**0.383 (0.208–0.704)**	
Age as Continuous			**0.973 (0.957–0.990)**
Sex			
Male	159 (77.9%)	ref	ref
Female	149 (79.2%)	1.081 (0.667–1.754)	1.106 (0.648–1.886)
Race/Ethnicity			
Non-Hispanic White	206 (77.4%)	ref	ref
Non-Hispanic Black	46 (79.3%)	1.117 (0.556–2.242)	1.080 (0.488–2.392)
Hispanic	44 (81.5%)	1.282 (0.609–2.698)	1.618 (0.652–4.016)
Non-Hispanic Other	6 (66.7%)	0.583 (0.141–2.399)	0.367 (0.076–1.773)
Missing	6		
Health Insurance			
Private	145 (80.6%)	ref	ref
Insurance NOS	16 (76.2%)	0.772 (0.265–2.252)	0.589 (0.190–1.833)
Medicaid and other public insurance	50 (76.9%)	0.805 (0.406–1.596)	0.718 (0.338–1.527)
Medicare	61 (75.3%)	0.736 (0.394–1.376)	1.106 (0.534–2.290)
No Insurance	23 (88.5%)	1.851 (0.525–6.514)	1.393 (0.357–5.426)
Missing	20		
Census Tract Residence **			
100% Urban	158 (74.9%)	ref	ref
100% Rural	28 (87.5%)	2.348 (0.787–7.004)	2.083 (0.616–7.048)
Mixed	118 (80.8%)	1.414 (0.844–2.369)	1.517 (0.776–2.965)
Missing	4		
Census Track Poverty ***			
Poverty <20%	262 (79.2%)	ref	ref
Poverty ≥ 20%	42 (72.4%)	0.691 (0.367–1.303)	0.629 (0.304–1.299)
Missing	4		
State of Residence			
State A **[61 (21%) TKI therapy]**			
State B	96 (80%)	ref	ref

Variables	CML cases with documented TKI therapy (excluding state A) N=393 n (%*)	Bivariate Analysis (excluding State A) OR (95% CI)	Multivariable Analysis (excluding State A) OR (95% CI)
State C	61 (84%)	1.271 (0.592–2.727)	1.771 (0.759–4.135)
State D	48 (75%)	0.750 (0.365–1.543)	0.872 (0.342–2.227)
State E	45 (80%)	1.023 (0.461–2.269)	1.438 (0.541–3.826)
State F	15 (52%)	0.475 (0.196–1.153)	0.602 (0.215–1.689)
State G	15 (75%)	0.750 (0.248–2.268)	0.665 (0.208–2.129)
State H	12 (80%)	1.000 (0.261–3.826)	0.658 (0.157–2.755)
State I	7 (70%)	0.583 (0.140–2.424)	1.365 (0.232–8.015)
State J	5 (83%)	1.250 (0.139–11.204)	0.644 (0.054–7.722)

*% of category tested that received TKI therapy as part of first course therapy

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Note: **Bolding** indicates significant finding