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Integrative Molecular Pathological Epidemiology of Congenital and Infant Acute Leukemia

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The Integrative Molecular Pathological Epidemiology of Congenital and Infant Acute Leukemia

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We hereby certify that this dissertation, submitted by Heather Williams conforms to acceptable standards and is fully adequate in scope and quality to fulfill the dissertation requirement for the degree of Doctor of Philosophy in Health Science.

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Abstract

Congenital and infant acute leukemia remain one of the most puzzling clinical issues in pediatric hematology-oncology. There is a paucity of studies focused on these rare, aggressive, acute leukemias; specifically, there is little study on the differences in disease in the youngest of infants less than 1 year of age unlike the numerous studies of the disease in older children. The United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer population registry program has been integral for a plethora of clinical population and pathology research studies for numerous diseases in the last 40 years and has an excellent resource for investigation of the infant population. Laboratory medicine and pathology professionals must use pathology results not only to diagnose individuals after the disease has been discovered, but the information must be applied retrospectively to develop new testing strategies. By classifying the intense heterogeneity within these cancers, the distinct changes of the diseases within individuals can be established, ultimately reshaping diagnostic methodologies. Through the application of Integrative Molecular Pathological Epidemiology to a 325-infant case series from the SEER program from 2008 to 2014, this dissertation study was used to evolve the classification of these pediatric cancers with the application of scientific nosology. This dissertation study has documented characteristics of this population for application in further precision medicine investigations to influence laboratory medicine algorithms for diagnosis and management of patients guiding health policy that are aimed at improving outcomes in the youngest of children.

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I dedicate this thesis to them.

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Chapter 1: Introduction

Introduction to the Chapter

Why does leukemia in infants continue to be one of the most puzzling clinical issues in pediatric hematology oncology? Leukemia in children under one year of age is rare, aggressive, and challenging due to complication risks and treatment toxicities generating great complexity in the diagnosis and management of this population (Brown, 2013). Even more daunting is the eventual outcome for too many of these children, which is death as relapse-free survival is poor in comparison with older children and adults (Brown, 2013).

The development frequency pattern of cancer subtypes in children is unique in comparison with the most common adult cancers (National Cancer Institute [NCI], 2013). As a result of the Pediatric Genome Project, Downing et al. (2012) suggested that cancer subtypes developing within adults and children may be discrete diseases due to etiologic differences and genomic variations, which generate their unique presentation between these populations (NCI, 2013). The National Cancer Institute's investment statement for pediatric cancer research indicated the intensity of heterogeneity within cancers may reflect the distinctive changes of the diseases at the molecular level (NCI, 2013). There are current estimates to suggest 20% of pediatric leukemia lack cytogenetic or molecular genetic markers to classify risk groups and nearly 60% of cases cannot be stratified by known markers for prognosis (Eidenschink Brodersen et al., 2016; NCI, 2013). This gap in the medical literature presents evidence that childhood leukemias are requiring new studies that will continue to evolve the classification of pediatric cancers (Cao et al., 2016; NCI, 2013).

Classification, often referred to as the "language of medicine," is fundamental for the description, definition, and terminology of disease (Swerdlow et al., 2008). Classification of disease must be clinically distinct, well-defined, and collectively exhaustive to ensure a

consensus is reported for appropriate diagnosis (Swerdlow et al., 2008). The World Health Organization (WHO) guidelines comprise clinical presentation, epidemiology, and pathology at diagnosis and disease course to yield disease classifications (Swerdlow et al., 2008). With the currently used WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues* and the newly released 2017 version, there is no recognition or proposal for the addition of a diagnostic category for infant leukemia (Swerdlow et al., 2008, 2017). More studies are necessary to associate the newly discovered characteristics of disease pathology to serve as the basis of emerging classifications of leukemia in young children (Cao et al., 2016; Swerdlow et al., 2008, 2017).

Given the lack of population-based studies that are focused on infant patients with acute leukemia, this investigator aimed to determine whether certain molecular pathology epidemiology (MPE) characteristics are associated with acute leukemia diagnosis in children under 1 year of age, defined in this dissertation study as an age restricted group of infants (<12 months). This investigator aimed to answer whether these MPE characteristics are associated with specific classifications of congenital (C) leukemia, classified in this dissertation study as less than 2 months of age, or infant (I) leukemia, classified as greater than or equal to 2 to less than 12 months of age, presenting as acute lymphoblastic leukemia (C-ALL or I-ALL), acute myeloid leukemia (C-AML or I-ALL), mixed phenotype acute leukemia (C-MPAL or I-MPAL) or other acute leukemia (C-OAL or I-OAL). These identified factors may influence laboratory medicine algorithms for diagnosis and management of these patients and identifying MPE characteristics that classify infant leukemia forms may guide health policy aimed at improving outcomes in the youngest of children.

Background to the Problem

Childhood cancers are one of the leading causes of death for children in the United States (US; Howlader et al., 2016; R. L. Siegel, Miller, & Jemal, 2016; D. A. Siegel et al., 2017) . Leukemia is the most common form of childhood cancer, which results from malignancy within the blood and bone marrow (Howlader et al., 2016; Popat, 2011; Roganovic et al., 2013). From 1975 to 2010, the incidence of childhood leukemia steadily increased by nearly 34% within the US (Howlader et al., 2016; Xie, Davies, Xiang, Robison, & Ross, 2003). In 2017, an estimated 3,000 cases of acute leukemia were diagnosed in children aged 0 to 14, accounting for 29% of all childhood cancers (R. L. Siegel et al., 2016). In comparison, estimated incidences for infant leukemia is 41 cases per million in the US or approximately 160 cases per year with AML accounting for 70 cases, and ALL accounting for an estimated 90 (Brown, 2013). As infant leukemia is extremely rare, the cases observed per year at even the largest pediatric leukemia centers are in the single digits; most often clinicians wait years between diagnostic cases, and this incidence has interfered with the advancement of expert knowledge regarding classification of infant leukemia forms (Brown, 2013).

International cooperative group studies have consistently reported that patients diagnosed with acute leukemia under 1 year of age have differing prognoses based age at diagnosis and whether the lymphoid or myeloid lineage is effected by the disease (Brown, 2013). The Interfant-99 study of I-ALL, which included patients aged 0 to 12 months in 22 countries from 1999 to 2005 reported a less than 50% four-year, event-free survival (EFS), which pales in comparison with childhood ALL, which includes children older than 1 year and has long term EFS rates of greater than 85% (Pieters et al., 2007). Comparatively, I-AML and older childhood AML outcomes are reported to be similar without regard to age by the AML subgroup of the Berlin-

Frankfurt-Münster (AML-BFM) cooperative group, an international study group founded in 1975, composed of scientific experts in pediatric leukemia and lymphoma from nearly 35 countries around the globe (Creutzig, Zimmermann, et al., 2012; Driessen et al., 2016; Pieters et al., 2007; van der Linden et al., 2009). The disparities in outcomes for C-AML, C-ALL, I-AML, and I-ALL patients treated with standard maximally intensive chemotherapeutic approaches and hematopoietic stem cell transplantation (HSCT), which remain curative for only a minority of patients, is the impetus for the need for additional studies, which may classify populations of infant leukemia (Brown, 2013; Hilden et al., 2006).

Hematopoiesis is an exquisitely regulated process requiring dynamic associations to ensure hematopoietic stems cells complete a complex system of lineage commitment, cellular differentiation, and maturation into diverse progenitor blood cells within the bone marrow (O'Brien, Vose, & Kantarjian, 2011; Orkin et al., 2015). Errors in various stages of blood component formation will result in the development of diverse leukemia subtypes (Kondo, 2010; Orkin et al., 2015). Aberrant differentiation, development, and replenishment of bone marrow will generate a unique presentation and clinical course of leukemia as either acute or chronic (Jan, Ebert, & Jaiswal, 2017; Orkin et al., 2015). Early stage immature white blood cells with aberrant development promote the rapid development of disease: acute leukemia (Jan et al., 2017; Orkin et al., 2015). The cellular lineage, lymphoid or myeloid, affected by the aberrant activity determines the leukemia subtype of acute lymphoblastic leukemia, acute myeloid leukemia, or mixed phenotype acute leukemia, involving both lineages (Kondo, 2010; Orkin et al., 2015). Due to the rapid development and presentation of acute leukemia, immediate and accurate diagnoses are necessary to manage these patients, a process highly dependent upon appropriate classification of leukemia forms (O'Brien et al., 2011; Orkin et al., 2015).

Classification of leukemia has evolved in the last 40 years to the currently accepted WHO guidelines (Swerdlow et al., 2017; Swerdlow et al., 2008). Proposed in 1976, the French-American-British (FAB) classification system was the first to distinguish AML from ALL, using morphological and cytochemical characteristics unique to the diseases (Bennett et al., 1976). The introduction of FAB classification is often championed as the critical event in the transition of hematology oncology from "nosologic chaos" into discrete classifications of disease (Heim & Mitelman, 2015). Nearly 10 years later, in 1986, the morphological, immunological, and cytogenetic (MIC) classification was introduced; however, traditional classifications continued to face criticism from the diagnostic community (Bennett et al., 1976). Introduced in 2001, the WHO *Pathology & Genetics Tumours of Haematopoietic and Lymphoid Tissues* was introduced and superseded all previous attempts by integrating available information into combined morphology classifications with newly emerging biological and genetic associations to advance the classifications of hematopoietic diseases into a practical nomenclature suitable for clinical use (Heim & Mitelman, 2015; Sandahl et al., 2015). With the revision to the WHO guidebook in 2008, there were integration of additional diagnostic criteria to classifications, introduction the first disease defining genetic abnormalities in the absence of morphology data, and great emphasis was placed on the pivotal role of cytogenetic abnormalities (Sandahl et al., 2015; Van den Berghe, 1988). In 2016, WHO released preliminary revisions for the new 2017 version, which are noticeably absent of further classification of infant acute leukemia; however, since previous versions, further genetic aberrations have been associated with leukemia, suggesting the discovery of differences in acute leukemia between childhood populations could be integrated into later versions (Cao et al., 2016; Sandahl et al., 2015; Van den Berghe, 1988).

In children from birth to 14 years, nearly 40% of all cancers are leukemia, and in children less than 5 years, leukemia is the major form of cancer (Howlader et al., 2016). Childhood leukemia is divided into three distinct forms: congenital, infant, and pediatric (M. Greaves, 2002; Roganovic et al., 2013). Age at cancer diagnosis determines the form of childhood leukemia (Roganovic et al., 2013). Congenital leukemia, also referred to as neonatal leukemia, develops within the first 4 to 6 weeks of life (Brown, 2013; Cao et al., 2016; Creutzig, van den Heuvel-Eibrink, et al., 2012; M. Greaves, 2002). Classification between congenital and infant leukemia is indistinct; approximate diagnosis at the age of 8 weeks or more to 12 months is infant leukemia (Brown, 2013; Cao et al., 2016; Creutzig, van den Heuvel-Eibrink, et al., 2012b; M. F. Greaves, 2002). Currently, the classification of congenital and infant leukemia may vary between the first 30 days of life (4 weeks), the first 4 to 6 weeks, and/or the first 8 weeks of life and may be grouped with all infant leukemia diagnoses under 1 year of age (Brown, 2013; van der Linden, Creemers, & Pieters, 2012). This investigator classified congenital leukemia from birth to less than 2 months, and infant leukemia from 2 months or less to 12 months of age. Pediatric leukemia is diagnosed in children over 12 months through late adolescence and 19 years or more; this investigator excluded diagnoses 12 months or more of age (Howlader et al., 2016; Roganovic et al., 2013).

Among childhood leukemia, there are major forms: ALL; AML; and minor forms, including MPAL; ALL accounts for approximately 76% of childhood leukemia and AML for approximately 24% of childhood leukemia with limited incidence of the emerging subtype MPAL (Bernard, Abdelsamad, Johnson, Chapman, & Parvathaneni, 2017; R. L. Siegel et al., 2017). This demographic information has correlated with a significant clinical burden of infants with acute leukemia with a unique presentations and classifications, which is likely associated

with their age at diagnosis. Although congenital and infant forms of ALL and AML share characteristics of clinical presentation and established genomic aberrations in pediatric and adult leukemia, many of these findings have predicted significantly worse outcomes for young infants rather than older patients (Downing et al., 2012; NCI, 2013; Pui & Evans, 1999; Pui et al., 2014).

Statement of the Problem

Leukemia is a heterogeneous disease, has a distinct presentation between forms, and previous scientific studies have uncovered limited factors known to contribute to aberrant hematopoiesis in leukemia diagnosed in children under 1 year of age (Bajwa, Skinner, Windebank, & Reid, 2004; Bresters et al., 2002; Brethon, Cave, Fahd, & Baruchel, 2016; Cao et al., 2016; De Lorenzo et al., 2014; Gerr et al., 2010; M. Greaves, 2002; Ibagy et al., 2013; Loeb & Arceci, 2002; Madhusoodhan, Carroll, & Bhatla, 2016; Masetti et al., 2015; McNeil, Cote, Clegg, & Mauer, 2002; Reaman et al., 1999; Ross, 1999; van der Linden et al., 2012; van der Linden et al., 2009; Zweidler-McKay & Hilden, 2008).

Congenital and infant leukemia have overlapping clinical characteristics but are unique in their epidemiology, clinical presentation, and pathology (Brown, 2009, 2013). Previous reports of infant leukemia in the literature are often indistinct from congenital forms as logically similar diseases are often classified, diagnosed, and managed similarly, making it quite difficult to identify the differences between infants in discrete congenital and infant populations. As congenital and infant forms of ALL and AML have been grouped together in previous evaluations, themes have emerged regarding prognostication of ALL versus AML diagnosed in infants under 1 year (Brown, 2013). The prognostication for AML and ALL is highly dependent upon features present at diagnosis with young age a predictor of an especially poor outcome in

ALL and conflicting reports of outcome in AML (Creutzig, Zimmermann, et al., 2012; Webb et al., 2001). The incidence of AML is higher than ALL in children under 1 year at diagnosis (Van der Linden et al., 2012). These differences in outcome based on age indicate there may be high risk factors in the younger population that contribute to adverse outcomes.

Numerous factors may influence disease susceptibility and pathology, including demographics, genetic factors, and environmental factors. In previous studies, there have attempts to identify the epidemiological factors responsible for these significant changes in incidence; however, due to the heterogeneous nature of leukemia, scientific studies have yet to fully delineate the underlying causes of aberrant hematopoiesis in young children and further work is needed (Duggan, Anderson, Altekruse, Penberthy, & Sherman, 2016; Hayat, Howlader, Reichman, & Edwards, 2007; Howlader et al., 2016). Understanding these MPE factors may affect the current classifications of leukemia in children under 1 year.

The emerging field of MPE has aimed to evaluate the etiologic heterogeneity of a disease population using transformative pathology findings to understand all stages of cancer evolution (Nishi et al., 2016; Ogino et al., 2012). The study of pathology records can assist with the classification of congenital and infant leukemia. Classifying the unique pathological presentations of each form of leukemia is critical to appropriate diagnosis, prognosis, and treatment. The pathology data of infants with leukemia have not been studied extensively, and further studies are needed.

Studies are needed to further classify acute leukemia and may identify diagnostic presentation, epidemiology, pathology, and treatment factors useful in attempts to reduce the mortality associated with aggressive forms. This investigator aimed to address whether information collected from infants under 1 year with leukemia generated a new classification

unique from older childhood and adult forms of the disease. Classifying the distinctive characteristics of congenital and infant leukemia can assist in the development of new diagnostic and management guidelines; alter prognostication; influence new personalized medicine interventions; and ultimately, positively affect survival rates for infants. With the development of new interventions, appropriate classification of congenital and infant leukemia is required, using patient factors known at presentation and through disease course discoverable via clinical research, using a retrospective evaluation of medical records deposited in a population-based registry.

The utilization of population based registries for the evaluation of rare diseases can provide data that are complementary to basic and clinical science studies and can assist in shaping the recommendations for real-world management of patients (Hulegardh et al., 2015). In the United States, the NCI's Surveillance, Epidemiology, and End Results (SEER) cancer population registry program is used to collect data about the diagnosis, treatment, and survival of disease (Duggan et al., 2016). In recent decades, the SEER database has been integral for a plethora of clinical population and pathology research studies (McNeil et al., 2002; NCI, 2010; Xie et al., 2003). SEER data are freely available to researchers, representative of approximately 28% of the U.S. population, collected from 18 geographic areas, and are most appropriate for the collection of clinical information for further stratification of disease (Duggan et al., 2016; NCI, 2010). Pathology data are recorded in routine clinical care, and submission is mandatory in SEER participating registry areas, but there remains a lack of studies that are used to combine these data in a sample study for improved classification of leukemia populations through the evaluation of medical record findings within a cancer registry (Duggan et al., 2016). Specifically, there is a paucity of studies that are focused on differences in disease in the youngest of infants

under 1 year of age with leukemia (Brethon et al., 2016; Brown, 2013; Cao et al., 2016; van der Linden et al., 2012; van der Linden et al., 2009).

Relevance

Since 1975, there have been substantial increases in the five-year survival rates for childhood leukemia (Howlader et al., 2016). This investigator aimed to address differences in outcomes for children with congenital and infant leukemia as recent increases in survival rates observed in childhood leukemia have been limited to children 1 year or more of age (Brethon et al., 2016; Brown, 2013; Cao et al., 2016; van der Linden et al., 2009; van der Linden et al., 2012). Children with congenital and infant leukemia have much poorer prognoses with overall survival (OS) for congenital forms near a mere 30% at 24 months post treatment when administered first line chemotherapeutics per international protocols (Bresters et al., 2002; Ferguson, Talley, & Vora, 2005). Dismal rates of survival for congenital leukemia are prolific in the scientific literature with numerous single case reports, documenting patient death prior to the administration of treatment (Bresters et al., 2002; Ferguson et al., 2005). The dearth of studies that are focused on the pathology of congenital and infant leukemia has hampered the improvement of clinical outcomes (Brethon et al., 2016; Brown, 2013; Cao et al., 2016; Somjee et al., 2002; Sonta-Jakimczyk & Szczepanski, 2003; van der Linden et al., 2009; van der Linden et al., 2012; Zweidler-McKay & Hilden, 2008).

Increased survival rates for children with leukemia since 1975 can be attributed to advances in clinical management hierarchies for this population, a direct result of advances in clinical nosology stemming from research on this population (Howlader et al., 2016). Modern approaches that are aimed at cancer control continue to evolve from classifications defined from distinct clinical presentation, epidemiology, and pathology factors that influence disease

development (Duggan et al., 2016; Howlader et al., 2016). Classification of disease is key to the appropriate prevention, screening, diagnosis, treatment, and monitoring of the patient population (Duggan et al., 2016; Howlader et al., 2016; Khoury et al., 2017). The medical record data for children diagnosed with leukemia from 1973 to 2014 is available from SEER (Duggan et al., 2016). Data from SEER and findings from this dissertation study present greater insight into the factors associated with leukemia disease development. Further characterization may influence the current standard for classifications and diagnoses of leukemia as reflected in the WHO guidelines for hematological neoplasms (Arber et al., 2016; Vardiman et al., 2009). Results from this dissertation study were used to generate congenital and infant leukemia patient subgroups, which can be used to influence classifications by WHO guidelines.

In the absence of research data that supports the creation of new classifications of congenital and infant leukemia, it will remain difficult to create personalized medicine modalities for these children. The use of pathology data from 2008 to 2014 presented an appropriate sample for studying emerging epidemiology, presentation, and pathology characteristics in infant leukemia populations. The SEER database has been previously utilized for the evaluation of an uncalculatable number of diseases, and the application of SEER data to study this population data fills a gap in the medical literature regarding infant leukemia.

The purpose of this dissertation study was to create a detailed classification of congenital and infant leukemia and investigate the epidemiology, the pathology of the disease course, and the reasons for differences in clinical outcome for these children. Leukemia has developed from a variety of biological and environmental factors, and this investigator sought to identify which factors may characterize congenital and infant forms of acute leukemia based on existing SEER pathology data. The findings of this dissertation study, using retrospective pathology data,

advanced the classification of leukemia, and the investigator reflected on how this information can enhance diagnosis and treatment of disease through the revision of clinical practice guidelines for the categorization and appropriate management of congenital and infant leukemia in newly diagnosed children (Gunnarsson et al., 2016; Howlader et al., 2016; Xie et al., 2003).

Elements

Theories

Scientific nosology. First introduced by Thomas Syndenham in the 17th century, the scientific ontology theory was built upon broad disease classifications known since Ancient Greece derived knowledge of underlying causes of disease, diagnostic features, or suitable treatments to form the basis of modern medical nosology (Burger, Davidson, & Baldock, 2008; Chute, 2000). Emerging scientific taxonomy first proposed by Carl Linnaeus for the classification of species has strongly influenced Sydenham's text, *Medical Observations Concerning the History and Cure of Acute Diseases,* in which he emphasized the need to reduce all diseases to distinct species to rival proposed phylogenies and phytologies of the time (Copeland, 1977). Sydenham along with Francois Boissier de Sauvages proposed that disease classifications be generated for entities with distinct characteristic symptoms and natural histories in order to enhance the care of patients via ontology (Hucklenbroich, 2014; Libby, 1922; Shershow, 1978).

In *The Birth of the Clinic*, Foucault suggested the drive to classify diseases by physicians was propelled by the desire to ensure sensible classifications systems can be applied to the clinic and are inclusive of the entire clinical spectrum of patient presentation for a given disease (Foucault, 1970; Hogan, 2013). Modern scholars began to integrate clinical observations in routine medical practice, and the nosological distinction of disease pathologies have burgeoned from the 1960s (Bowker & Star, 1999; Fleck, 1979; Foucault, 1970). Through 1960 to 1980, the

complexities of classification systems for clinical diagnoses grew and were led by the geneticist Victor McKusick's who wrote *Mendelian Inheritance in Man* (MIM), a catalog of human genetic diseases that ensured disease classifications began to include descriptions of detectable underlying genetic abnormality (Hogan, 2013; McKusick, 1966). McKusick (1966) introduced a new theory of disease pathology nosology inclusive of genetics in stark contrast to previous associations of disease stating, "phenotypic overlap is not necessarily any basis for considering them [clinical diseases] fundamentally the same or closely related," diverging the course of clinical nosology in the decades to come (McKusick, 1966. p. xi).

As disease nosology steadily grew from 1980 and 1999, the integration of molecular conceptions of the human genome and known diseases strongly influenced how information regarding disease pathology and subsequent nosology were integrated into classification systems, often providing clinical delineation for previous flaws in existing nosological systems (Hogan, 2013; Smolik, 1999). With the completion of the Human Genome Project in 2003, a shift in clinical and laboratory practice occurred, and Rose (2007) argued the shift towards a "molecular gaze" had a central role in the development of disease pathology nosology. Gaudillière and Rheinberger (2002) contended the boom of biomedicine is based largely on the central role of molecular analyses and contended that knowledge gained in the laboratory had started to replace the pathology clinic as the focus area for finding new medical knowledge. Competing perspectives theorized that the combination of laboratory and clinic practices in pathology generate "bioclinical collectives," which would have a transformative impact on the production of medical knowledge necessary for disease classification (Hogan, 2013; Rabeharisoa & Bourret, 2009). Hucklenbroich (2014) contended the central theoretical concepts of all clinical nosology classifications introduced must include "objectively determinable pathological conditions" with

justification of an exact definition of disease entities. Scientific nosology theory is used to drive research focused on the study of disease, etiologies, and pathogenesis, which leads to the revision of disease categorization and the continuous emergence of new classifications of disease based on the integration of descriptive pathology and clinical data. These factors were investigated in this dissertation study.

Sufficient-Component cause model. First proposed by Rothman in 1976, the sufficient-component cause model (SCCM) presents a theoretical basis for research of causation in disease development while simultaneously providing a conceptual model of the necessary conditions for disease development and prevention in an individual and for studies of epidemiology causes of diseases in groups (Aschengrau & Seage, 2014; Rothman, Greenland, & Lash, 2008). Sufficient causes of disease are not single entities, but rather a "complete causal mechanism" composed of a minimal set of factors and circumstances termed "component causes" when present will inevitably result in the disease process or "completion of the sufficient cause" (Aschengrau & Seage, 2014; Rothman et al., 2008). SCCM presents that sufficient component causes or those that are absolutely necessary or "necessary component causes" must be present for disease development even in the absence or presence of other component causes (Aschengrau & Seage, 2014; Rothman et al., 2008). The first major facet of SCCM presents that the inhibition of a component cause ensures the completion of sufficient cause for disease development is inhibited (Aschengrau & Seage, 2014; Rothman et al., 2008). Secondly, SCCM presents that the biological onset of the disease occurs synonymously with completion of the sufficient cause; the onset of disease symptoms or clinical presentation do not necessarily occur simultaneously with this event (Aschengrau & Seage, 2014; Rothman et al., 2008). Lastly, SCCM presents component causes may act distant in time, meaning causal component causes can occur at any time during

an individual's life (Aschengrau & Seage, 2014; Rothman et al., 2008). The SCCM may serve as the basis for investigations into acute leukemia development in children under 1 year, including identification of additional component causes, inhibitive events, and/or disease symptoms or clinical presentation of disease; these factors were investigated in this dissertation study.

Molecular pathological epidemiology. Molecular pathology epidemiology has emerged as a new transdisciplinary field in 2010 as proposed by Shuji Ogino and Meir Stampfer to link the role of biomedical, epidemiology, pathology, and health status into research for clinical outcomes (Ogino & Stampfer, 2010). MPE has converged traditional epidemiology and pathology research disciplines to investigate how exposures influence carcinogenesis, identify molecular pathology events associated with tumor initiation or progression, and show how interplay between these factors influence disease etiology and prognosis (Ogino et al., 2016). With a basis in traditional epidemiology, research that is focused on the investigation of factors known to increase the risk of disease and transitional pathology, the focus of research is primarily on the investigation of histopathologic and molecular signatures so that MPE integrates numerous laboratory medicine diagnostic strategies with epidemiology study and clinical pathology outcomes (Ogino et al., 2016; Ogino & Stampfer, 2010).

MPE is influenced by the precision medicine framework inclusive of the unique disease principle that theorizes each individual undergoes distinct pathogenic processes, including genetic and epigenetic changes, cellular interplay, and external exposures and is compounded by influential factors of diet, environment, microbial, and lifestyle (Nishi et al., 2016; Ogino et al., 2016; Ogino & Stampfer, 2010). Based on epidemiologic methodology, MPE includes the study of risk factors, pathologies, and populations of disease (Ogino & Stampfer, 2010). MPE has been

applied to study numerous diseases but has been most commonly applied to neoplasia, given the accessibility of diagnostic test results routinely used in clinical care.

Studies applying MPE are used to synthesize data from epidemiology, clinical presentation, and pathology of diseases (Lazcano-Ponce et al., 2001; Ogino, Chan, Fuchs, & Giovannucci, 2011; Ogino et al., 2012; Ogino et al., 2016). The application of MPE to colorectal neoplasia, a group with similar heterogeneity to acute leukemia, has uncovered molecular characteristics of disease that have reshaped the laboratory diagnostic methodologies used for testing the disease (Nishi et al., 2016; Ogino et al., 2012; Ogino et al., 2016). MPE studies indicated that mutations in specific genes were responsible for a majority of aggressive colorectal cancers, allowing for targeted rather than generalized laboratory diagnostics and classification based on this prognostic factor in financially limited resource environments (Nishi et al., 2016; Ogino et al., 2012; Ogino et al., 2016). As medicine advances into the era of personalized prevention and medicine for diseases in the individual patient, the application of MPE to uncover the simultaneous role of molecular, pathology, and epidemiology into an integrative science will link these alterations to the genome to generate a framework for the development of the disease using population based studies (Ogino et al., 2012).

A newly emerging discipline, Integrative Molecular Pathological Epidemiology Comparative Effectiveness Research (I-MPE-CER) was used in this dissertation study to evaluate unique epidemiology and demographic characteristics of children with congenital and infant leukemia, and show pathology characteristics linked to cancer evolution of patient subgroups of congenital and infant leukemia (Ogino et al., 2012; Ogino et al., 2016; Ogino & Stampfer, 2010). The use of I-MPE-CER in this dissertation study was used for the appropriate subgrouping of patients based on disease similarities to maximize efficacy and effectiveness in

pediatric hematology-oncology diagnostics and public health policy for clinical care (Ogino et al., 2016; Ogino & Stampfer, 2010).

Social ecology theory. Social ecology theory (SET) developed from 1965 to 1975 has focused on relationships between the social, institutional, and cultural contexts of individual-environment interactions and is an inherently interdisciplinary approach to research in health care (Binder, Stokols, & Catalano, 1975; Stokols, 1996). Cassel (1964) urged social and health scientists to develop a new framework to investigate the influences of social and culture events on health and pave the way for further study and interpretations of individual-environment associations.

Assumptions of SET present that the physical and social environments of the individual influence the health status observed (Stokols, 1992, 1996; Stokols, Allen, & Bellingham, 1996). The physical environment, such as geographical location, accessibility to care, and advanced treatment technologies, may influence health with the same power as genetic heritage, patterns of individual behavior, or psychological disposition (Stokols, 1992). The scale and complexity of the environment is formed from component elements: (a) physical and social components, (b) objective (actual) or subjective (perceived qualities) and (c) scale or immediacy to individuals and groups. Although independent, the characteristics of each environmental attribute are relevant and ultimately serve to influence the final health outcome (Stokols, 1992, 1996; Stokols et al., 1996). Application of SET has a requirement for multiple levels of analysis and diverse methodologies; the integration of numerous disciplines of medicine with public health generates an interface to facilitate influence on the health of individuals and populations (Stokols, 1992, 1996; Stokols et al., 1996). SET is rooted in systems theory, which accounts for the interdependencies of immediate and distant environments in coordination with the dynamic

interrelations between individuals and environments; cycles of influence between individuals and their environment occur with outcomes directly influencing both parties (Stokols, 1992, 1996; Stokols et al., 1996). SET has been applied to study multiple facets of the environment, including physical, social, cultural issues and their influence upon individual health outcomes (Catalano, 1979; Emery & Trist, 1972). Previous application of SET research findings include the introduction of environmental interventions, such as water fluoridation programs to reduce tooth decay and health education programs focused on tobacco's association with cancer to reduce cigarette smoking with implementation of research findings in specific populations identified through investigations (Stokols et al., 1996).

Investigating the characteristics of a given community that may affect the diagnosis and outcome of the disease, SET is applied in attempt to understand the interaction between the environment and the patient (Catalano, 1979; Emery & Trist, 1972). Should a significant proportion of disease diagnoses occur in a given geographical area, these diagnoses may imply an environmental impact and association with disease outcomes (Catalano, 1979; Emery & Trist, 1972). Socio-economic status can contribute to the diagnosis of disease, affect access to care, and influence the outcome as measured by mortality; documenting the characteristics of the area by poverty level, unemployment status, family income, and foreign-born individuals may show how interactions with the environment influence the incidence of acute leukemia in the infant population.

The use of SET in this dissertation study were used to ensure interventions in pediatric hematology oncology was appropriately targeted for maximum impact to patient care. Combining multilevel method analysis in the evaluation of individual-environment interactions as applied to social issues, SET was applied to the evaluation of epidemiology, presentation, and

pathology of congenital and infant leukemia in this dissertation study (Whiteley, 1999). In the application of SET, there were numerous factors considered that influence the clinical presentation and disease course of congenital and infant leukemia in the US in children under 1 year of age (Whiteley, 1999). The investigator documented the current understanding of clinical presentation and disease course for infants through an evaluation of MPE characteristics that can be linked to social, institutional, and cultural issues that may change patient outcomes. In geographical areas where social economic factors may influence the ability for patients to gain access to additional therapies needed to increase survival outcomes for infants with leukemia, modifications to standards of care, including the application of more aggressive therapies as a first line treatment, may be warranted, given the subtype of leukemia as a result of SET theories. Additional changes to clinical paradigms may include altering treatment methodologies based on the patient's ethnic or genetic heritage documented at diagnosis, generating personalized treatment based on documented demographics via laboratory testing, which has changed the patient's disposition for acute leukemia. Applying SET to the infant leukemia population could influence the diagnostic techniques and treatment modalities given considerations to environmental conditions indicated during the MPE classification of the disease.

Implementation science in laboratory medicine. Laboratory medicine was first recorded by the Ancient Greek physician Hippocrates near 300 BC as he examined human bodily fluids in an attempt to understand disease pathology (D. Berger, 1999). In 1896, Johns Hopkins Hospital opened the first true clinical laboratory of the modern era, which lead to development of diagnostic tests critical during disease epidemics of the early 20th century; therefore, laboratory medicine became integral in clinical medicine (M. R. Williams, Lindberg, Britt, & Fisher, 1984). Today, there are more than 200,000 clinical laboratories that provide testing services in the US

alone (The Lewin Group, 2008). Research about the value and impact of laboratory medicine tests is limited in the medical literature, a finding in stark contrast to data that are suggestive that these diagnostic tests are integral to many clinical decisions (Horvath, 2013; Kaul et al., 2017; Khoury et al., 2017; The Lewin Group, 2008).

The utilization of diagnostic testing in laboratory medicine has a requirement for clinical validity with clinical and cost effectiveness (Horvath, 2013; Khoury et al., 2017). A test is clinically valid if it can present highly accurate diagnostic and/or prognostic data crucial for clinical decisions (Farkas, 2016; Horvath, 2013). A test is clinically effective if it has a positive impact on patient outcomes (Farkas, 2016; Horvath, 2013). Cost-effective laboratory tests are defined by their contributions to reducing health care costs (Farkas, 2016; Horvath, 2013). The implementation of evidence-based laboratory medicine (EBLM) into the clinical management of patients is dependent upon the availability of research evidence regarding the appropriate use of laboratory investigations combined with physician clinical expertise and consideration of the needs, expectations, and concerns of the individual patient (Horvath, 2013).

Gray (1997) proposed that laboratory professionals have a responsibility to (a) eliminate poor or useless tests before widespread implementation or “stop starting”; (b) eliminate old tests without benefit or cause harm, termed “start stopping”; and (c) implement new tests when evidence is suggestive that their efficacy and effectiveness or “start starting or stop stopping” in order to provide the best benefit to the patient. Although widely adopted across the discipline, these basic principles of laboratory medicine do not represent the true implementation science for new tests and/or the revision of laboratory test repertoires as it is often a daunting and challenging task (Gray, 1997; Horvath, 2013). To ensure that EBLM will result in the equitable provision of services, clinicians, patients, policymakers, laboratory scientists, and researchers

must contribute to the appropriate utilization of medical tests through evaluation of current tests used in clinical medicine (Horvath, 2013; Khoury et al., 2017). The use of implementation science in this dissertation study was used for the evaluation of diagnostic tests currently used in pediatric hematology-oncology, influence clinical policies, and affect laboratory testing algorithms.

Research Questions

The literature regarding infant leukemia, particularly the development in the youngest of infants with congenital or neonatal leukemia, is limited. The focus of this dissertation study was on documenting the characteristic differences between congenital and infant forms of acute leukemia. To add to the clinical literature, to provide insight into the disease presentations, generate epidemiological profiles, and to consider possible modifications to laboratory algorithms, the following research questions were addressed:

Question 1. What is the distinctive clinical presentation of children diagnosed with congenital and infant AML and ALL under 1 year of age in the SEER database between 2008 to 2014 in the United States?

- Question 1.1. Are there distinctive clinical presentations of children diagnosed with congenital AML and ALL at 1 and 2 months of age?

Question 2. What is the epidemiological profile of cases of congenital and infant leukemia AML and ALL in the SEER database between 2008 to 2014 in the United States?

- Question 2.1. What is the proportion of congenital AML and ALL in 1 to 2-month-old infants?

- Question 2.2. What is the proportion of infant AML and ALL in 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12-month-old infants?
- Question 2.3. What is the proportion by sex of congenital AML, congenital ALL, infant AML, and infant ALL?
- Question 2.4. What is the proportion by SEER registry region of congenital AML, congenital ALL, infant AML, and infant ALL?
    - Question 2.4.1. What are the characteristics of the highest proportion SEER registry region counties (where diagnosed) by families below poverty (100% of federal poverty level [FPL]), persons below poverty in county (100% FPL), number unemployed in county, median family income, and number of foreign born individuals?
- Question 2.5. What is the cause of death (COD) proportion by congenital AML, congenital ALL, infant AML, and infant ALL?

Question 3. How do the characteristics of AML and ALL differ, addressing differences in mortality over time between 2008 to 2014 in the United States?

- Question 3.1. How do the mortality rates among congenital AML, congenital ALL, infant AML, and infant ALL differ during this period?
- Question 3.2. What are the differences in treatment administered among congenital AML, congenital ALL, infant AML, and infant ALL during this period?

Question 4. How could new pathology subgroups of congenital AML, congenital ALL, infant AML, and infant ALL generate new laboratory testing algorithms?

Question 5. How could new pathology subgroups of congenital AML, congenital ALL, infant AML, and infant ALL affect the need for laboratory tests that provide non-specific and specific results that aid in diagnosis and management?

Hypotheses

Leukemia presentation, disease course, treatment selection, and clinical outcome are unique in young children. These differences in disease are likely associated with patient and disease epidemiology. Given differences between congenital, infant, pediatric, and adult acute leukemia population outcomes, the investigator hypothesized to document statistically significant characteristics in the SEER sample that are associated with the diagnosis of discrete forms of acute leukemia in the under 1 year of age infant population.

Definitions of Terms

1. Hematopoiesis. Throughout life, blood cellular components are constantly produced and replenished through the process of hematopoiesis (Jagannathan-Bogdan & Zon, 2013).
2. International classification of childhood cancer. The international classification of childhood cancer (ICCC) is a standardized methodology for the categorization of malignancies diagnosed in childhood.
3. International classification of diseases for oncology. The international classification of diseases for oncology (ICD-O) is a standard classification that establishes rules, nomenclature, and codes of disease pathology that conform to the current edition of World Health Organization's *Classification of Tumours of Haematopoietic and Lymphoid Tissues*.

4. International Classification of Diseases for Oncology. The international classification of diseases for oncology is a standard classification that establishes rules, nomenclature, and codes of disease pathology that conform to the current edition of World Health Organization's *Classification of Tumours of Haematopoietic and Lymphoid Tissues*.
5. Leukemia. Errors in the process of hematopoiesis result in leukemia. Within the bone marrow, leukemia results from inappropriate differentiation, development, and replenishment of blood forming cells (Kondo, 2010). Distinct forms of leukemia include acute and chronic as characterized by the speed of clinical presentation and aberrant process responsible for disease development (Kondo, 2010). Acute leukemia is divided by the altered cellular lineages: lymphoid, myeloid, or mixed phenotype lymphoid/myeloid (Kondo, 2010). With the rapid development of leukemia, acute leukemia results from the accumulation of aberrant early stage immature white blood cells (Kondo, 2010). Acute leukemia forms include acute lymphoblastic leukemia, acute myeloid leukemia, or mixed phenotype acute leukemia. With the slow development of leukemia, chronic leukemia results from the accumulation of aberrant mature white blood cells (Kondo, 2010). Chronic leukemia forms include chronic lymphoblastic leukemia and chronic myeloid leukemia.
    - Congenital leukemia. Congenital leukemia is the diagnosis of leukemia in children from birth to under 2 months of age (Bresters et al., 2002).
    - Infant leukemia. Infant leukemia is the development and diagnosis of leukemia in children aged greater than or equal to 2 to under 12 months (Bresters et al., 2002).

- Pediatric leukemia. Pediatric leukemia is the development and diagnosis of leukemia in children aged greater than or equal to 1 to under 19 years (Bresters et al., 2002).

6. Surveillance, epidemiology, and end result program**.** A program governed by the NCI, the SEER has information on cancer diagnoses, has a database of diagnostic data, and has cancer statistics data that are aimed at reducing the U.S. population cancer burden. The SEER database is freely accessible for health care research with valuable information collected for diagnosis, treatment, and outcome of cancer patient populations.
7. World Health Organization's *Classification of Tumours of Haematopoietic and Lymphoid Tissues*. The World Health Organization's *Classification of Tumours of Haematopoietic and Lymphoid Tissues* is a reference text routinely used as a concise resource for diagnostic information regarding all hematopoietic and lymphoid neoplasms.

Description of Variables

The dependent variable is the risk of acute leukemia diagnosis in children under 1 year of age, and the survival from acute leukemia was evaluated in this dissertation study. The independent variables, which are the demographic features of children diagnosed with leukemia under 1 year of age, include age at diagnosis; sex; race; lineages of leukemia; International Classification of Diseases for Oncology ICD-O-3 WHO 2008 classification; and International Classification of Childhood Cancer ICD-O-3 WHO 2008 classification, diagnostic confirmation technique, disease primary site, number of primary tumor sites, immunophenotype designation, and the administration of treatments).

Age at diagnosis is a calculated variable and is presented as age in months derived from birth date in months subtracted from diagnosis date in months as entered in the SEER registry. Sex is presented as female or male. Race is classified as per the SEER registry: (a) Caucasian (White), (b) African American (Black), (c) Asian or Pacific Islander, and (d) American Indian or Alaska Native. Ethnicity was classified as per the SEER registry: Hispanic or non-Hispanic. Leukemia is presented as ALL, AML, MPAL or OAL. ICD-O-3 WHO 2008 classification was evaluated using the four digit disease code/behavior code, which is 9911/3 and 9911 for AML and a simple explanation of the pathology subtype, which is for AML (megakaryoblastic) with t(1,22) (p13;q13); *RBM15-MKL1* and /3 for a malignant disease within the primary site of the diagnosed disease. The ICCC ICD-O-3 WHO 2008 classification is presented as the broad subgroup of leukemia to ensure agreement with the ICD-O-3 WHO 2008. The disease diagnostic confirmation methodology is representative of the technique required to confirm acute leukemia as a diagnosis in the patient sample, such as the observation of the descriptive anatomy of cells and tissues within the diagnostic sample observed via light microscopy. The disease primary site is presented as the location within the body of the primary disease aligned to the ICD-O-3 code. The immunophenotype is the representation of the characterization of the cellular proteins expressed on the surface of cells within the diagnostic sample and designates the specific leukemia lineages. The administration of treatment describes the types of therapy or therapies administered for treatment. Covariates include the SEER registry of diagnosis, county of diagnosis, state of diagnosis, type of reporting source, insurance status, persons age 18 under in diagnosis county, families below poverty (100%) within diagnosis county, unemployed individuals within diagnosis county, median family income within the county, and number of foreign born individuals within the county.

Rationale

The SEER database is a robust resource frequently used for population-based studies of disease. Congenital and infant forms of leukemia are understudied diseases, and additional studies are needed. Diagnoses of congenital and infant leukemia across the US are recorded within the SEER database at designated registry centers. Duggan et al. (2016) proposed pathology professionals increase the utilization SEER to evolve the application of the data to numerous diseases, suggesting that the use of population registries to evaluate disease is critical to understanding the future applicability of the SEER research. The use of the SEER database to study congenital and infant leukemia presented a sample to evaluate and report characteristics that contribute to the medical literature and ensure the classification of leukemia in children under 1 year is complete.

Assumptions

Medical record data of children diagnosed under 1 year of age can be accessed from the NCI SEER program. Information submitted to SEER is collected from various institutes across the US as entered by health professionals, following administration of care into the patient primary medical record (NCI, 2010). The coding and placement of the medical record data is performed by SEER Data Management System Professionals (DMSPs) employed at each registry site (NCI, 2010). During the coding and data placement process, DMSPs must enter patient information anonymously and with great fidelity. Access to patient medical information used in this dissertation study was limited to anonymized unique SEER record ID for each diagnosis event. The investigator assumed that all appropriate laboratory medicine and pathology testing performed via clinical guidelines has been dutifully requested and deposited into the patient medical record. Data entry, coding, and transfer to the SEER registry was assumed to be

accurate with minimal record errors and no significant impact on the results of this dissertation study.

Summary of the Chapter

As a part of the diagnostic care process, pretreatment assessment of leukemia patients based on classification linked to risk stratification of disease subtype significantly affects the selection of treatment course. The WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues*, generally used to classify leukemia, has been integral in the diagnostic care process; however, it lacks specific subgroups for children with congenital and infant leukemia. A study of the demographic profiles of children with leukemia under 1 year of age collected from the SEER database was used in the development of classifications of congenital and infant forms of the disease.

A retrospective study was used to assess the association of patient demographic profile on emerging leukemia subtypes in patients under 1 year of age using population-based data. This dissertation study used the SEER data diagnosed from 2008 to 2014. This dissertation study has contributed to the knowledge of leukemia classification, has generated profiles of patient stratification for laboratory diagnostic algorithms, and affected clinical management paradigms, which will improve the clinical outcome of children with the disease.

Chapter 2: Review of the Literature

Introduction to the Chapter

The desire for clinicians to classify leukemia has evolved and advanced with the field of medicine. However, the discovery and widespread report of leukemia in the infant population would take until the turn of the 20th century to appear in the medical literature. As case reports of congenital and infant leukemia was emerging from clinicians around the globe, a congenital hematologic malignancy was rejected by many clinicians and pathologists while pediatricians were confused by the disease presentation due to a lack of differentiation between diseases in younger and older children in the medical literature (Hjelt & Wegelius, 1956). Because of the confusion, teams of clinicians and laboratory medicine professionals were motivated to address the lack of classification in an attempt to reduce the ambiguity in diagnosis.

The earliest combinatory classification systems, the French-American-British (FAB) and the morphological, immunologic, cytogenetic (MIC) had emerged from 1970 to 1989, which linked laboratory medicine specialties to provide the most accurate diagnoses with available techniques of the time (Bennett et al., 1976; First MIC Cooperative Study Group, 1986; Lilleyman, Hann, Stevens, Eden, & Richards, 1986; van den Berghe, 1988; van Eys et al., 1986). The FAB and MIC classifications were robust classifications given the technologies of the time but limited the ability to classify many known forms of disease (Sandahl et al., 2015). FAB was relying heavily upon morphology, and MIC was stressing the importance of chromosomal abnormalities and cellular markers to enhance appropriate diagnoses (First MIC Cooperative Study Group, 1986; Lilleyman et al., 1986). Yet both the FAB and MIC classifications had failed to incorporate all known underlying biological causes and clinical characteristics of homogenous malignancies in the medical literature at the time (Sandahl et al., 2015; Vardiman, Harris, &

Brunning, 2002). However, as laboratory medicine diagnostics advanced, the need for additional classification criteria became apparent, and the World Health Organization (WHO) released a combined pathology and genetics classification system in 2001, which standardized the nomenclature with relevance to clinical diagnostics (Sandahl et al., 2015; Vardiman et al., 2002).

Leukemia diagnoses in the infant population are rare, and the revised version of the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues* does not address additional nuances of the standard workup including integration of all laboratory medicine findings to ensure accurate and timely diagnoses. The current WHO classifications for congenital and infant leukemia have recognized only a combinatory infant form of the disease based on previous studies that rarely differentiated between these populations to evaluate differences in pathology, epidemiology, treatment, and outcomes. Previously identified differences between infants and children at disease presentation are currently used for risk stratification of infant leukemia and rely heavily on pathology and age differences to stratify prognoses of children for treatment modalities. This investigator aimed to address this gap in the classification system by applying integrative molecular pathology epidemiology to the SEER population registry to direct appropriate laboratory diagnostic testing and enhance personalized treatments.

Historical Overview

Leukemia discoveries. Ancient Egyptians provided the first written description of cancer in approximately 1600 BC, but only after nearly three and one-half millennia, in the 1800s, did the discovery and early understanding of leukemia enter the medical literature (Kampen, 2012; Piller, 2001; Pui, 2012). The discovery of leukemia is often attributed to four clinicians: Alfred Armand Louis Marie Velpeau, Alfred François Donné, John Hughes Bennett, and Rudolf Ludwig Karl Virchow, individuals who contributed to the discovery and early history of the

disease (Beutler, 2001; Degos, 2001; Kampen, 2012; Kiple, Graham, Frey, & Browne; Lichtman, 2008). There remains no consensus on who may claim the discovery of leukemia as these clinicians each contributed to the advancement of the early medical understanding of leukemia in unique ways (D. Berger, 1999; Kampen, 2012; Piller, 2001). Velpeau was the first to describe the symptoms and clinical presentation of leukemia in 1825 (Kampen, 2012; Velpeau, 1825). Donné pioneered microscopy based study of leukemia, documented his first patient observations in *cours de microscopie* [microscope course] in 1844, and subsequently wrote an atlas of microscope examinations in leukemia with visual descriptions and illustrations linked to the uniquely altered blood composition within patients with leukemia (Donné, 1844; Donné & Foucault, 1845; Kampen, 2012). In 1845, Bennett was the first clinician to document and attribute abnormalities and excess accumulation of leucocytes in the blood to the new disease, leucocythemia, correctly identifying the disease as a disorder of the blood system (Bennett 1860; Kampen, 2012). Virchow's seminal manuscript *weisses blut* [white blood], released in 1845, documented the disease as a reversed balance of white and red blood cells in the body with an accumulation of white blood cells and coined the term "leukämie [leukemia]" to describe the disorder (Kampen, 2012; Virchow, 1856). Virchow continued to investigate leukemia, and in 1856, theorized a cellular original of leukemia and was the first to distinguish various forms of the disease that form the basis of current subtypes of the disease (Kampen, 2012; Piller, 2001). However, the first diagnosis of leukemia in childhood in a 9-year-old girl was reported in London by Henry Fuller in 1850 (Pui, 2012).

Pathology and laboratory medicine advanced rapidly in the late 1800s with Ernst Neumann's hypothesis that leukemia was a disease of the bone marrow in 1872, which led to the introduction of the bone marrow puncture technique by Friedrich Mosler in 1876 and

histochemical staining methodologies introduced by Paul Ehrlich in 1877, which introduced widespread leukocyte differentiation testing at diagnosis, which would become the foundation for the classification of leukemia into the 1900s (Pui, 2012). Following the discrimination of myeloblasts and lymphoblasts by Nägeli in 1900, leukemia was soon classified into four subtypes by 1913: acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphoblastic leukemia, and chronic myeloid leukemia (Piller, 2001; Pui, 2012). The following year, Boveri (1914) theorized that chromosomal changes generated the framework for genetic instability, a requirement for cellular changes associated with malignant transformation and the subsequent development of cancer. As the clinical presentation of leukemia using laboratory medicine was documented in the medical literature by the early 1900s, the search for understanding the basis of distinct forms of leukemia were used to drive the revolution to classify the various forms of the disease.

The classification of leukemia originally included pathology, morphology, and clinical presentation of the disease, but advances in laboratory medicine continued throughout the century. Introduced in 1934, flow cytometry was established as a critical tool in distinguishing the leukemic lineage by immunophenotypic features of the aberrant cells prior to classification (Moldavan, 1934; Weir & Borowitz, 2001). Boveri's theory of chromosomal basis of abnormalities formed the foundation of cytogenetics, a new laboratory medicine discipline that emerged as a critical component of pathology testing in the early 1960s to 1965. Through the modern era, classification systems were emerging that incorporated diagnostic techniques of numerous laboratory medicine disciplines. Today, leukemia diagnoses depend upon integrated pathology data, including morphology, cytochemistry, immunophenotyping, and cytogenomics (Swerdlow et al., 2017).

First reports of leukemia in the infant population. Although leukemia in childhood has been documented in the medical literature since the late 1800s, references to leukemia in infants slowly was emerging in the early 1900s with little definition between presentation of disease based on age in childhood groups (Churchill, 1904; Holsclaw, 1918; Koch, 1922; Smith, 1921; Stransky, 1925). The first documentations of acute leukemia relied upon physical examinations, blood studies, and in many cases post-mortem evaluations of the infant patients (Churchill, 1904; Koch, 1922; Smith, 1921; Stransky, 1925). The reliance of leukemia diagnosis upon only morphology and histochemistry limited the classification of leukemia subtypes, but major themes emerged. Acute forms of leukemia in children dominated the literature with few reports of chronic leukemia in children (Bernhard, Gore, & Kilby, 1951; Churchill, 1904). It soon became apparent that unlike adults, the majority of leukemia cases in children were of the acute forms: ALL and AML with swift presentation and death (Piller, 2001; Pui, 2012). Dr. Frank S. Churchill at the University of Chicago summarized the known reports of leukemia early in life in the 1800s, suggesting that although rarely recognized previously, the disease would become recognizable by all given the newly emerged blood examination techniques of the time (Churchill, 1904).

Dr. J. H. Mason Knox, Jr. (1913) at Johns Hopkins University reported the youngest case of AML in an infant aged 9 months based on pathology information derived from differential blood count and morphology with diagnosis occurring only after a short 10-day disease course and subsequent death; an earlier report of a newborn with a likely congenital form of leukemia was documented by Pollman but without bone marrow examination and limited blood work, the diagnosis was not confirmed (Mason Knox, 1913; Pollman, 1898). The first confirmed report of congenital AML was documented by Koch in a still born infant (Koch, 1922). The earliest report

of congenital ALL was documented by Tancré (1918) in a child aged 1 month with death by age 4 months. Dr. Weld Smith at Harvard reported the youngest case of congenital ALL in an infant aged 6 weeks with initial disease presentation to a clinician reported at 3 weeks, and signs of leukemia present as early as birth; the patient presented with advanced disease and progressed rapidly and died at 8 weeks of age (Smith, 1921). Holsclaw (1918) documented via post mortem the first confirmed diagnosis of infant ALL in an infant aged 11 months; an earlier report of infant ALL by Jewett (1901) occurred with limited workup, but the diagnosis was not confirmed.

By 1939, Kelsey and Anderson confirmed that a mere nine reported cases of congenital leukemia in the literature were acceptable to the standards of the time with eight confirmed cases of congenital AML and one of ALL (Abt, 1937; Kelsey & Andersen, 1939). Kelsey and Anderson (1939) established the skewed ratio of AML to ALL in the congenital infant population that continues to be represented today (Howlader et al., 2016). Nearly 40 years following the first case of leukemia in young infants, there remained confusion regarding the criteria for congenital leukemia (Bernhard et al., 1951). Bernhard et al. (1951) reviewed early reports of leukemia within infants from 1920 to 1950, suggesting that many previous reports could be more accurately reclassified as other disorders easily confused with leukemia: erythroblastosis fetalis, congenital syphilis, or sepsis. Bernhard et al. (1951) described specific criteria to fulfill a diagnosis of congenital leukemia: (a) the presence of a leukemic state at birth shortly after birth or up to 6 weeks of age at diagnosis; (b) findings of spontaneous hemorrhages of skin and mucous membranes, nodular skin infiltration, enlargement of the spleen and liver, adenopathy, fever, and pallor; (c) evaluation of the blood should indicate alteration of the marrow through demonstration of an inappropriate portion of poorly differentiated or undifferentiated cells, a finding that should be confirmed via bone marrow evaluation; (d) a

general finding of increased white blood cells with an concomitant decrease in red cells and platelets; (e) serological studies to rule out erythroblastosis fetalis and congenital syphilis.

Following publication by Bernhard et al. (1951), only 18 cases in the medical literature met the accepted criteria of the time for congenital leukemia (Baumann, 1950; Bernhard et al., 1951; Büngeler, 1931; Cross, 1944; Giblin, 1933; Hamme, 1944; Kelsey & Andersen, 1939; Koch, 1922; Kornmann, 1934; Morrison, Samwick, & Rubinstein, 1939; Smith, 1921; Stransky, 1925; White & Burn, 1931). However, confusion over the classification of infant leukemia continued as a fundamental text in clinical hematology and case reports of infant leukemia published from 1950 to 1953 failed to document the appropriate number of congenital leukemia cases in the literature without recognition of this distinctive disease from other infant forms (Wintrobe, 1951). Clinicians continued to report cases of congenital leukemia within and outside of these criteria set forth by Bernhard et al. (1951), adding confusion to the literature (Shindo & Shibantani, 1957; Soderhjelm & Ranstrom, 1951). By 1954, O'Connor, McKey, and Smith (1954) confirmed the findings of Bernhard et al. (1951), and less than 20 cases of acute leukemia were present in the clinical literature. Cases of acute infant leukemia in the medical literature were also linked to birth anomalies, including Down's syndrome, a finding that today has produced a distinct classification of myeloid proliferations Related to Down syndrome in the current WHO classification. Hjelt and Wegelius (1956) insisted that although congenital leukemia was of exceedingly rare occurrence, those well-established authors who continued to deny the existence of the rare entity should refer to the authenticated cases that left no doubt of congenital and infant forms of leukemia in young children. However, subsequent case reports upon infants with leukemia have failed to clearly distinguish the demographic characteristics of infant and congenital forms of acute leukemia.

Between 1955 to 1975, the classification of leukemia advanced rapidly, driven by the explosion of transformative integration of human genetics into pathology practice in early 1960 (Lindee, 2002; Rowley, 1978). Ford, Jacobs, and Lajtha (1958) reported the first chromosomal abnormalities within bone marrow cells from patients with acute leukemia. Following the discovery in 1961 of the first chromosomal abnormality in a leukemic form, which was the Philadelphia chromosome in chronic myeloid leukemia by Nowell and Hungerford, genetics was to become an integral part of classifying leukemia (Moorhead, Nowell, Mellman, Battips, & Hungerford, 1960; Nowell, 1962; Nowell & Hungerford, 1960, 1961). However, it was not until the introduction of a chromosome banding technique by Caspersson, Gahrton, Lindsten, and (1970) that chromosomal abnormalities could be precisely identified by chromosome number, chromosome arm, and chromosome region (Caspersson et al., 1970). Rowley (1973a) identified the first balanced translocation in a patient with AML between chromosomes 8 and 21 or t(8;21)(q22;q22), adding cytogenetics to the standard workup of patients with acute leukemia (Rowley, 1973a, 1973b, 2009). Following Rowley's discovery, a steady increase in the number of characteristic chromosomal abnormalities were described in hematological diseases, including the first chromosomal abnormalities: t(8;16)(p11;p13) in AML, t(15;17)(q22;q21) in acute promyelocytic leukemia (APL), and t(4;11)(q21;q23) in ALL, which established a new criteria for leukemia classification and the genetics of the disease (Benedict, Lange, Greene, Derencsenyi, & Alfi, 1979; R. Berger, Bernheim, Weh, Daniel, & Flandrin, 1979; Cimino, Rowley, Kinnealey, Variakojis, & Golomb, 1979; Garson, 1979; Hagemeijer, van Zanen, Smit, & Hahlen, 1979; Huang, Gomez, Kohno, Sokal, & Sandberg, 1979; Liang, Hopper, & Rowley, 1979; Rowley, 1979; Rowley, 1980; Lindgren & Rowley, 1977; Mitelman et al., 1979; Morse, Hays, Peakman, Rose, & Robinson, 1979; Oshimura, Freeman, & Sandberg, 1977; Prigogina et

al., 1979; Rowley, 1977, 1979; Rowley, Golomb, & Dougherty, 1977; Secker-Walker, Swansbury, Lawler, & Hardisty, 1979; Trujillo, Cork, Ahearn, Youness, & McCredie, 1979).

The geneticists McKusick, Mitleman, and Levan with many other scientists advocated for nearly 30 years for a global acceptance in clinical medicine that "genetic factors are involved in all diseases," further cementing the role of genetic testing in diagnostics as demonstrated by the findings in hematologic disease and other malignant disorders between 1980 to 2000 (see Table 1; McKusick, 1969, p. 11; Mitelman, 1980; Mitelman & Levan, 1976).

Table 1
Gene Fusion in Neoplasia Reported 1980 to 1999

Years	Hematologic disorders	Solid tumors	Total*
1980-1989	19	0	19
1990-1994	55	14	69
1995-1999	101	38	139
2000-2004	162	63	220
2005-2009	247	150	294
2010-2014	379	1220	1598
Total*	674	1379	2038

Note. Based on data contained in Mitleman database. Adapted from *Chromosomal Translocation and Genome Rearrangements in Cancer,* by J. Rowley, M. M. Le Beau, and T. H. Rabbitts, 2015, Zurich, Switzerland: Springer International Publishing. Copyright 2015 by Springer International Publishing. *The total number of abnormalities discovered does not add up as each fusion is only counted once although it may be found in numerous distinct disease entities.

The Earliest Classification Systems

French-American-British classification. The earliest classification system for acute leukemia emerged in 1976 from the French-American-British (FAB) Co-Operative Group, composed of seven hematologists (Bennett et al., 1976). This uniform system of classification and nomenclature of acute leukemia resulted from the expert review of 200 cases using peripheral blood and bone marrow films that demonstrated the accurate recording of reference

standards of morphology and cytochemistry results that characterized cell types and groups of the disease (Bennett et al., 1976). The FAB group concluded that acute leukemia could be divided into lymphoblastic and myeloid forms that were first divided into three and six subgroups, respectively (Bennett et al., 1976). The FAB classification introduced objectivity, improved the uniformity of diagnoses, and established the first common language for health professionals in the evaluation of leukemia. Using the revised FAB classification system, ALL cases were now divided into three forms and AML into eight forms (see Table 2). However, given the advancement of other pathology services, including immunophenotyping and genetics, the FAB types of acute leukemia failed to incorporate all of findings during a standard evaluation of a patients suspected of having leukemia and other classifications soon emerged.

Table 2
Classification of Acute Leukemia According to the Revised French-American-British Criteria

FAB type	Brief description	Percentage of all diagnoses with this subtype
	Acute lymphoblastic leukemia	
L1 (children)	Morphology: homogeneous small sized blasts with round nuclei. Scant cytoplasm is observed generally without vacuoles.	82%
L2 (older children and adults)	Morphology: heterogeneous large sized blasts with irregular nuclei. Variable cytoplasm is observed generally with abundant vacuoles.	15%
L3 (patients with leukemia secondary to Burkitt's lymphoma)	Morphology: homogeneous moderate-large sized blasts with regular nuclei. Moderate cytoplasm is observed generally with prominent vacuoles.	3%

(continued)

FAB type	Brief description	Percentage of all diagnoses with this subtype
	Acute myeloid leukemia	
M0	Morphology: mature cells are not generally observed; non-distinguishing features and diagnosis requires immunologic identification. Immunophenotyping: CD13+/-, CD15+ or CD33+/-, CD34+, dimCD45+, CD38+, and CD3-, CD10-, CD19- and CD5- (B or T lineage markers).	2%
M1	Morphology: minimal maturation observed; distinguishing features include agranular blasts and infrequent Auer rods. Immunophenotyping: CD13+/-, CD14+/-, CD15+, CD33+, CD34+, HLA-DR+ and CD3-, CD10-, CD19- and CD5- (B or T lineage markers).	10%-18%
M2	Morphology: maturation observed; distinguishing features include blasts and frequent Auer rods. Immunophenotyping: CD13+/-, CD33+, CD34+ (myeloid-associated markers), HLA-DR+/- and CD3-, CD10-, CD14-, CD19- and CD5- (B or T lineage markers).	27%-29%
M3	Morphology: proliferating abnormal promyelocytes observed; distinguishing features include frequent abundant Auer rods. Immunophenotyping: CD13+, CD33+, HLA-DR-, CD3-, CD10-, CD14-, CD19- and CD5- (B or T lineage markers).	5%-10%
M4	Morphology: differentiation of both myeloid and monocytic lineages observed; distinguishing features include frequent monocytes and promonocytes. Immunophenotyping: CD11b/c+, CD13+, CD14+, CD33+, HLA-DR+ and CD3-, CD10-, CD14-, CD19- and CD5- (B or T lineage markers).	16%-25%
M5	Morphology: differentiation of monocytic lineage observed; distinguishing features include frequent large monoblasts. Immunophenotyping: CD11b+, CD33+, CD64+, HLA-DR+ and CD4-, CD34-, CD14-, CD19- and CD5- (B or T lineage markers).	13%-22%
M6	Morphology: distinguishing features include frequent nucleated red blood cells with extreme dysplastic features present. Immunophenotyping: Glycophorin A+, CD71+, and CD34-, CD45-, MPO-.	1%-3%
M7	Morphology: distinguishing features include atypical megakaryocytes with fibrotic marrow. Immunophenotyping: CD34+, dimCD117+, CD36+, dimCD41+, dimCD61+, CD33+ and CD13-, MPO-.	4%-8%

(continued)

FAB type	Brief description	Percentage of all diagnoses with this subtype
	Mixed phenotype acute leukemia	
B/myeloid T/myeloid B/T and myeloid (tri-lineage)	Morphology: Blasts from more than one lineage or blasts with co-expression of antigens from more than one lineage; generally, there are two populations resembling myeloblasts and lymphoblasts. May also present as a single population resembling ALL. Immunophenotyping: MPO+, CD117+, CD13, CD33, and/or CD2, CD7.	<4% (all MPAL)

Note. Adapted from "The World Health Organization (WHO) classification of the myeloid neoplasms," by J. W. Vardiman, N. L. Harris, and R. D. Brunning, 2002, Blood, *100*(7), p. 2293. Copyright 2002 by American Society of Hematology.

Morphological, immunologic, cytogenetic classification. Proposed in 1986, the MIC classification was the first pathology classification system that attempted to incorporate long established morphological findings in acute leukemia and myelodysplastic diseases with immunologic and genetic findings (First MIC Cooperative Study Group, 1986; van den Berghe, 1988). The MIC classification resulted from a series of MIC workshops that focused upon the open discussion of data accumulated after the introduction of FAB system, which indicated further classifications could have diagnostic and prognostic value (First MIC Cooperative Study Group, 1986). The MIC classification introduced 10 subtypes of acute leukemia based upon their unique characteristics from multiple laboratory pathology disciplines and was revised again in 1988 (First MIC Cooperative Study Group, 1986; van den Berghe, 1988). From 1976 to late 1990s, the FAB and MIC classifications of leukemia were widely used, but the discoveries in genetics remained separate from the classification of hematologic malignancies.

Not until 1999 did the WHO recognized the pivotal role of cytogenetic abnormalities, which emphasized the utilization of genetic testing in diagnostic testing and a new classification emerged for leukemia, which allowed for the first differentiation between AML subtypes in the WHO *Pathology & Genetics of Tumours of Haematopoietic and Lymphoid Tissues, 2001*

(Vardiman et al., 2002). The previous FAB and MIC classifications, which only partially differentiated between morphologically and immunologically similar groups of leukemic cells had become the driving factors for the generation and revision of the WHO classification that incorporated the ability to discern genetic differences in the leukemia to advance clinical diagnostic abilities (see Table 3; Pui, 1995; Swerdlow et al., 2008; Vardiman et al., 2002).

Table 3
WHO Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues Classification 2001 of Subgroups and Subtypes

Acute myeloid leukemia Alkylating agent related	Chronic myeloproliferative neoplasms
AML with recurrent cytogenetic abnormalities	Chronic myelogenous leukemia
AML with t(8;21)(q22;q22.1); *(AML1(CBFa)/ETO)*	Chronic neutrophilic leukemia
AML with abnormal bone marrow eosinophils inv(16)(p13q22) or t(16;16)(p13;q22); (*CBFb-MYH11)*	Chronic eosinophilic leukemia/hypereosinophilic syndrome
APL (AML with t(15;17)(q22;q12) (*PML-RARa)* and variants	Polycythemia vera
AML with 11q23 (*MLL*) abnormalities	Chronic idiopathic myelofibrosis
AML with multilineage dysplasia	Essential thrombocythemia
AML and Myelodysplastic syndromes, therapy related	Chronic myeloproliferative disease, unclassifiable
	Myelodysplastic/myeloproliferative diseases
Topoisomerase II inhibitor-related	Chronic myelomonocytic leukemia
AML not otherwise specified categorized	Atypical chronic myeloid leukemia
AML with minimally differentiated	Juvenile myelomonocytic leukemia
AML without maturation	Myelodysplastic/myeloproliferative disease, unclassifiable
AML with maturation	Myelodysplastic syndromes
Acute myelomonocytic leukemia	Refractory anemia
Acute monoblastic and monocytic leukemia	Refractory anemia with ringed sideroblasts
Acute erythroid leukemia	Refractory cytopenia with multilineage dysplasia
Acute megakaryoblastic leukemia	Refractory anemia with excess blasts
Acute basophilic leukemia	Myelodysplastic syndrome, unclassifiable
Acute panmyelosis with myelofibrosis	Myelodysplastic syndrome associated with isolated del(5q) chromosome abnormality

(continued)

Acute myeloid leukemia Alkylating agent related	Chronic myeloproliferative neoplasms
Myeloid sarcoma	Pre-cursor B- and T-cell neoplasms
Acute Leukemia of ambiguous lineage	Pre-cursor B-lymphoblastic leukemia/lymphoma
	Pre-cursor T-lymphoblastic leukemia/lymphoma

Note. Adapted from "The World Health Organization (WHO) classification of the Myeloid Neoplasms." by J. W. Vardiman, N. L. Harris, and R. D. Brunning, 2002, *Blood*, *100*(7), p. 2292. Copyright 2002 by American Society of Hematology.

Current Classification Systems

The development of WHO classifications aimed to address diagnostic issues with the FAB and MIC classifications. In particular, between the 2001 *Pathology & Genetics Tumours of Haematopoietic and Lymphoid Tissues* and the 2008 *Classification of Tumours of Haematopoietic and Lymphoid Tissues* versions, it became clear that FAB and MIC classifications failed to recognize the overlapping morphology and immunophenotyping between distinct genetic entities (Pui, 2012). The first edition of WHO classifications (2001) incorporated many of these genetic differences discovered in the preceding 40 years (see Table 3). However, due to the rapid advancement of genetic technologies in the 2000s, the WHO (2001) soon required an immediate update, which was issued in 2008 (see Table 4 and Table 5).

Table 4
2008 WHO Classification of Myeloid Neoplasms and Acute Leukemia for Subgroups and Subtypes

Acute myeloid leukemia and related neoplasms	Myeloproliferative neoplasms
AML with recurrent genetic abnormalities	Chronic myelogenous leukemia, BCR-ABL1 positive
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Chronic neutrophilic leukemia
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Polycythemia vera
APL with *PML-RARA*	Primary myelofibrosis
AML with t(9;11)(p21.3;q23.3); *MLLT3*-KMT2A(MLL)	Essential thrombocythemia
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	Chronic eosinophilic leukemia, NOS

(continued)

Acute myeloid leukemia and related neoplasms	Myeloproliferative neoplasms
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*	Mastocytosis
AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*	Myeloproliferative neoplasm, unclassifiable
Provisional entity: AML with mutated *NPM1*	Myelodysplastic/myeloproliferative neoplasms
Provisional entity: AML with biallelic mutations of *CEBPA*	Chronic myelomonocytic leukemia
Provisional entities: AML with BCR-ABL1 and AML with mutated *RUNX1*	Atypical chronic myeloid leukemia, BCR-ABL1 negative
AML with myelodysplasia-related changes	Juvenile myelomonocytic leukemia
Therapy-related myeloid neoplasms	Myelodysplastic/myeloproliferative neoplasms, unclassifiable
AML not otherwise specified (NOS)	Provisional entity: refractory anemia with ring sideroblasts and thrombocytosis
AML with minimal differentiation	Myelodysplastic syndromes
AML without maturation	Refractory anemia with unilineage dysplasia
AML with maturation	Refractory anemia
Acute myelomonocytic leukemia	Refractory neutropenia
Pure erythroid leukemia	Refractory thrombocytopenia
Acute megakaryoblastic leukemia	Refractory anemia with ring sideroblasts
Acute basophilic leukemia	Refractory cytopenia with multilineage dysplasia
Acute panmyelosis with myelofibrosis	Refractory anemia with excess blasts
Myeloid sarcoma	Myelodysplastic syndrome associated with isolated del(5q)
Mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2); BCR-ABL1	
Mixed phenotype acute leukemia with T/myeloid, NOS	
Mixed phenotype acute leukemia with t(v;11q23.3); KMT2A rearranged	
Provisional entity: NK cell lymphoblastic leukemia/lymphoma	

Note. Adapted from "The 2008 Revision of the World Health Organization (WHO) Classification of Myeloid Neoplasms and Acute Leukemia: Rationale and Important Changes," by J. W. Vardiman, J. Thiele, D. Arber, R. D. Brunning, M. J. Borowitz, A. Porwit, . . . and C. D. Bloomfield, 2009, *Blood, 114*(5), p. 939.

Table 5
2008 WHO Classification of Precursor Lymphoid Malignancies

Subgroups	Subtypes
B-lymphoblastic and leukemia/lymphoma, NOS	B-lymphoblastic and leukemia/lymphoma with hyperdiploidy
B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities	B-lymphoblastic and leukemia/lymphoma with hypodiploidy
B-lymphoblastic and leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1*	B-lymphoblastic and leukemia/lymphoma with t(5;14)(q31;q32); *IGH-IL3*
B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *MLL* rearranged	B-lymphoblastic and leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22); *TEL-AML1 (ETV6-RUNX1*)	T-lymphoblastic leukemia/lymphoma

Note. Adapted from "The 2008 Revision of the World Health Organization (WHO) Classification of Myeloid Neoplasms and Acute Leukemia: Rationale And Important Changes," by J. W. Vardiman, J. Thiele, D. Arber, R. D. Brunning, M. J. Borowitz, A. Porwit, . . . C. D. Bloomfield, 2009, *Blood*, *114*(5), p. 939. Copyright 2009 by American Society of Hematology.

With the most recent WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues* version, released in late 2017, there was recognition that chromosomal abnormalities in AML can overlap with one or more FAB groups; t(15;17) is found in FAB M3, whereas AML with t(8;21)(q22;q22.1) *RUNX1-RUNX1T1* is found in both FAB M2 or M4. AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22) *CBFB-MYH11* is found in FAB M4 or M5, AML with t(6;9)(p23;q34.1) *DEK-NUP214* is found in both FAB M2 or M4, and AML with *BCR-ABL1* is found in M1 and M2, ALL, and MPAL (see Table 6 and Table 7).

Table 6
2017 WHO Classification of Myeloid Malignancies

Acute myeloid leukemia and related neoplasms	Myeloproliferative neoplasms
Acute myeloid leukemia with balanced translocations/inversions	Chronic myelogenous leukemia, *BCR-ABL1* positive
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Chronic neutrophilic leukemia
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Polycythemia vera
APL with *PML-RARA*	Primary myelofibrosis Prefibrotic/early PM Overt primary myelofibrosis
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL) variant *KMT2A* translocations in acute leukemia	Essential thrombocythemia
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	Chronic eosinophilic leukemia, NOS
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*	Myeloproliferative neoplasm, unclassifiable
AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*	Mastocytosis
AML with *BCR-ABL1*	Cutaneous mastocytosis
Acute myeloid leukemia with gene mutations	Systemic mastocytosis
AML with mutated *NPM1*	Mast cell sarcoma
AML with biallelic mutations of *CEBPA*	Myelodysplastic/myeloproliferative neoplasms
AML with mutated *RUNX1*	Chronic myelomonocytic leukemia
AML with myelodysplasia-related changes	Atypical chronic myeloid leukemia, *BCR-ABL1* negative
Therapy-related myeloid neoplasms	Juvenile myelomonocytic leukemia
AML NOS	Myelodysplastic/myeloproliferative neoplasm refractory anemia with ring sideroblasts and thrombocytosis
AML with minimal differentiation	Myelodysplastic/myeloproliferative neoplasms, unclassifiable
AML without maturation	Myelodysplastic syndromes
AML with maturation	MDS with single lineage dysplasia
Acute myelomonocytic leukemia	MDS with ring sideroblasts
Acute monoblastic and monocytic leukemia	MDS with multilineage dysplasia

(continued)

Acute myeloid leukemia and related neoplasms	Myeloproliferative neoplasms
Pure erythroid leukemia	MDS with excess blasts
AML without maturation	MDS with excess blasts and erythroid predominance
AML with maturation	MDS with excess blasts and fibrosis
Acute myelomonocytic leukemia	Myelodysplastic syndrome associated with isolated del(5q)
Acute monoblastic and monocytic leukemia	Myelodysplastic syndrome, unclassifiable
Pure erythroid leukemia	Childhood myelodysplastic syndrome
Acute megakaryoblastic leukemia	refractory cytopenia of childhood
Acute basophilic leukemia	Myeloid neoplasms with germline predisposition
Acute panmyelosis with myelofibrosis	Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction
Myeloid sarcoma	Acute myeloid leukemia with germline *CEBPA* mutation
Myeloid proliferations related to Down syndrome	Myeloid neoplasms with germline *DDX41* mutation
Transient abnormal myelopoiesis associated with Down syndrome	Acute myeloid leukemia with germline *CEBPA* mutation
Myeloid leukemia associated with Down syndrome	Myeloid neoplasms with germline *DDX41* mutation
Blastic plasmacytoid dendritic cell neoplasm	Myeloid neoplasms with germline predisposition and pre-existing platelet disorders
Acute leukemias of ambiguous lineage	Myeloid neoplasms with germline *RUNX1* mutation
Acute undifferentiated leukemia	Myeloid neoplasms with germline *ANKRD26* mutation
Acute leukemias of ambiguous lineage	Myeloid neoplasms with germline *ETV6* mutation
Acute undifferentiated leukemia	Myeloid neoplasms with germline predisposition with a pre-existing disorder or organ dysfunction
Mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2); *BCR-ABL1*	Myeloid neoplasms with germline *GATA2* mutation

(continued)

Acute myeloid leukemia and related neoplasms	Myeloproliferative neoplasms
Mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2); *BCR-ABL1*	Myeloid neoplasms with germline *GATA2* mutation
Mixed phenotype acute leukemia with t(v;11q23.3); *KMT2A* rearranged	Myeloid neoplasms with germline predisposition associated with inherited bone failure syndrome syndromes and telomere biology disorders
Mixed phenotype acute leukemia with B/myeloid, NOS	
Mixed phenotype acute leukemia with T/myeloid, NOS	
Mixed phenotype acute leukemia, NOS, rare types	
Acute leukemias, NOS	

Note. Adapted from "The 2016 Revision of the World Health Organization Classification of Myeloid Neoplasms and Acute Leukemia," by D. Arber, A. Orazi, R. Hasserjian, J. Thiele, M. J. Borowitz, M. M. Le Beau, . . . J. W. Vardiman, 2016, *Blood*, *127*(20), p. 2392. Copyright 2016 by American Society of Hematology.

Table 7
2017 WHO Classification of Precursor Lymphoid Malignancies

Subgroup	Subtype
B-lymphoblastic and leukemia/lymphoma, NOS	B-lymphoblastic and leukemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH-IL3*
B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities	B-lymphoblastic and leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-lymphoblastic and leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1*	B-lymphoblastic and leukemia/lymphoma, *BCR-ABL1-like*
B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged	B-lymphoblastic and leukemia/lymphoma with iAMP21
B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*	T-lymphoblastic leukemia/lymphoma
B-lymphoblastic and leukemia/lymphoma with hyperdiploidy	Early T-cell precursor lymphoblastic leukemia
B-lymphoblastic and leukemia/lymphoma with hypodiploidy	NK cell lymphoblastic leukemia/lymphoma

Note. Adapted from "The 2016 Revision of the World Health Organization Classification of Myeloid Neoplasms and Acute Leukemia," by D. Arber, A. Orazi, R. Hasserjian, J. Thiele, M. J. Borowitz, M. M. Le Beau, . . . J. W. Vardiman, 2016, *Blood*, *127*(20), p. 2392. Copyright 2009 by American Society of Hematology.

Morphologic examination remains a gold standard in establishing an appropriate diagnosis and is the primary diagnostic test used in the selection of further studies in a query leukemia specimen, but the modern classification requires appropriate integration of morphology, immunophenotype, and cytogenomic findings prior to a confirmatory diagnosis (Heim & Mitelman, 2015).

Today, the leukemia classification systems continue to continuously undergo revision and refinement to advance the medical understanding of acute leukemia using genetic pathology; although the disease in infants has been documented for nearly a century, the distinction between congenital and infant leukemia remains unclear. Further studies are needed using data collected during the standard workup of congenital and infant leukemia to classify these diseases more appropriately. The aim of this dissertation study was to address the need to further classify congenital and infant leukemia using standard workup data collected in the SEER database.

Leukemia Diagnoses

Standard workup. Infant leukemia may present with fairly non-specific signs and symptoms of disease, which are variable between patients (Van der Linden et al., 2012). The fundamental sign of infant leukemia in 50% of the cases is the observation of the so-called "blueberry muffin baby," a consequence of leukemia cutis created from cutaneous leukemia infiltrates that have a generalized distribution of firm blue, red, or purple nodules on the infant (Bas Suarez et al., 2011; Van der Linden et al., 2012). However, the presentation of leukemia cutis occurs in a number of other infant diseases, including malignancies and infections. The differential requires a standard workup for confirmation (Van der Linden et al., 2012). Additionally, a true leukemia must be differentiated from transient myeloproliferative disorder (TMD), a common disease in children with Down syndrome, but rare reports have been

described in children without Down syndrome (Van der Linden et al., 2012). Nearly 80% of patients present with hepatosplenomegaly with enlargement of the liver more frequent than enlargement of the spleen; comparatively, enlargement of the lymph nodes is observed in approximately 25% of infants (Van der Linden et al., 2012). Half of all patients will present with fever, a consequence of tumor cell cytokine release and/or infection; the presence of leukemic cell accumulation within the bone, resulting in the common finding in young children of bone and joint pain; and in the infant child that lacks communication skills, which may present as an inconsolable child (Van der Linden et al., 2012). If leukemia is suspected in an infant, standard of care requires an immediate referral to a pediatric hematologist-oncologist to ensure differential diagnoses can be immediately ruled out (Van der Linden et al., 2012).

Specimen collection. In a patient with a query new acute leukemia, an evaluation of the peripheral blood is rapid, readily performable via phlebotomy, and is an inexpensive test, which can warrant the need for additional testing based on the percentage of circulating blast cells at diagnostic presentation (Pui, 2012; Weinkauff et al., 1999). To establish a confident diagnosis of leukemia, a bone marrow examination is essential due to known morphologic differences between leukemic cells within the peripheral blood and bone marrow; in addition, known discrepancies between the peripheral blood and bone marrow are common as approximately 20% of patients with acute leukemia do not have circulating blasts cells at diagnosis (Pui, 2012; Weinkauff et al., 1999). To obtain a bone marrow for evaluation, a bone marrow aspirate must be collected via an invasive procedure, performed by trained clinicians, and for children, deep sedation administered by an anesthesiologist, which increases the costs associated with an already costly procedure; the collection site chosen for aspiration is highly dependent upon the age and size of the patient (Malempati, Joshi, Lai, Braner, & Tegtmeyer, 2009). Bone marrow

aspirates are generally obtained from the posterior superior iliac crest; however, for infants younger under 1 year of age, the anteromedial surface of the tibia is occasionally used for specimen collection (Malempati et al., 2009; Pui, 2012). The collection of bone marrow involves a painful and costly procedure, and the appropriate triage of the sample for subsequent diagnostic tests is crucial in the appropriate care of newly diagnosed acute leukemia patients (Malempati et al., 2009; Pui, 2012; Weinkauff et al., 1999).

Bone marrow morphologic/cytochemical analysis. The initial classification of leukemia starts with morphologic evaluation of specimens prepared from peripheral blood and bone marrow smears or biopsy touch preps to generate stained air-dried slides (Pui, 2012). The completion of a morphological diagnosis is divided into two major steps: establish a diagnosis of leukemia and classification using the lineage and degree of cellular differentiation to determine the leukemia form (Pui, 2012). In numerous cases, the diagnosis of leukemia requires an evaluation and correlation between the findings observed in the peripheral blood and bone marrow via morphology and full blood counts as the presence or absence of abnormal leukemic cells observed in the peripheral blood may be variable (Pui, 2012). Upon routine workup, acute leukemia patients often present with anemia and thrombocytopenia, resulting from bone infiltration via the leukemic process, whereas leukocyte counts may be decreased or vary widely in range of increases dominated by the presence of blasts; the presentation of leukemia may vary as a subset of patients present with cytopenia in the absence of blasts (Pui, 2012). Although morphologic examination may allow for appropriate initial assessment and classification of some forms of leukemia, many findings following cytochemical staining are ambiguous and require immunophenotyping in order to preliminarily classify the leukemia via the traditional FAB type, a system that provides a framework for the WHO classification that is reliant upon appropriate

subsequent genetic evaluation of disease prior to complete and integrated diagnosis (Pui, 2012). Of note, the strong relationship between FAB type and WHO classification for AML continues; however, use of FAB in ALL has become obsolete as the ability to discriminate overlapping features of leukemia from lymphoma is very poor (Pui, 2012).

Immunophenotyping. The integration of immunophenotyping or flow cytometric analysis into routine diagnostic laboratories has decreased the utilization of traditional cytochemical staining with morphological evaluation (Pui, 2012). Instead, modern flow cytometric analysis via immunophenotyping has allowed for improved identification and classification of ALL and AML. Flow cytometric analysis is used to in the recognition of two major subtypes of ALL: precursor B-cell (B-lymphoblastic) and pre-cursor T-cell (T-lymphoblastic) leukemia/lymphoma and can differentiate all eight AML FAB subtypes M0-M7 (Pui, 2012). These subtypes are divided by their characteristic expression of specific cellular markers that can be detected via flow cytometry (Pui, 2012).

Cytogenomic testing. Cytogenetic and molecular genetic testing (termed "cytogenomic" herein) are standard components of a query acute leukemia specimen workup (Rowley, 2009; Swerdlow et al., 2017). Conventional cytogenetics is the process of chromosome analysis via banding techniques, and molecular genetic analysis is the examination of the genome via DNA or RNA in leukemic cells. Genetic alterations known to be associated with acute leukemia can be detected using combined conventional cytogenetics and molecular genetic analyses. Cytogenomic analysis has improved the identification and classification of ALL and AML using biologically and clinically significant disease subtypes that have been incorporated into WHO classifications that have prognostic implications for congenital and infant leukemia but have not been specifically associated with these populations.

Relevant Theory

Current classifications for congenital and infant leukemia. With the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 and the recently issued 2017 revision, there is no recognition for a distinct entity for congenital or infant acute leukemia. There remains a shortage of molecular pathology epidemiology data regarding congenital and infant leukemia groups to further characterize similarities and differences between these unique groups. This investigator contributed to this classification gap and identified risk factors in the youngest population of children that contribute to their adverse outcomes that can be detected during the initial appropriate diagnosis of these diseases.

Current Understanding of Leukemia in Infants

ALL and AML differ in the average age of populations commonly affected by the diseases; children and adolescents are the majority of ALL diagnoses, whereas adults are the majority of AML diagnoses (Pui, 2012). In children under 1 year of age at diagnosis, ALL accounts for more cases than AML; however, in the congenital leukemia population defined in the literature, AML dominates ALL in diagnoses (Aier, Zadeng, Basu, Biswal, & Nalini, 2002; Bajwa et al., 2004; Brown, 2009; Campos et al., 2011; Özdemir, Çaksen, Þahin, Çiftçi, & Çỳkrỳkçỳ, 2002; Raj et al., 2014; Shah, Mehta, Desai, & Shah, 2003; Sung, Lee, Kim, & Jun, 2010; Wiemels, 2012). Bresters et al. (2002) and Issacs (2003) reviewed 117 and 145 patient records, respectively, and reported nearly 56% to 64% of congenital diagnoses were AML and 21% to 38% ALL, a finding consistent with even the earliest reports of infant and congenital leukemia in the literature (Bernhard et al., 1951; Bresters et al., 2002; Heerema et al., 1999; Isaacs, 2003; O'Connor et al., 1954; Pui, 2012; Pui et al., 2014; Resnick, Hampel, Fishel, & Cohn, 2009; Wolk, Stuart, Davey, & Nelson, 1974).

Laboratory medicine and pathology of leukemia in infants less than 1 year. In the infant population under 1 year of age, particular subtypes of ALL and AML are more frequent (Van der Linden et al., 2012). Although ALL and AML in the infant population have been comprehensively reported, the distinction between the congenital and infant leukemia population has not been extensively researched. The paucity of medical literature that differentiate congenital and infant leukemia pathology characteristics when reporting information on leukemia in young children has interfered with ability to classify these distinct entities.

In an epidemiological review of childhood leukemia, Ross, Davies, Potter, and Robinson (1994) focused largely on the distinction between older children and infants. Ross et al. (1994) stated that infant leukemia posed a unique topic for epidemiologic studies of hematopoietic neoplasms, given their distinct biological characteristics in stark comparison to leukemia presentation and course in children and adults. Although Ross et al. (1994) provided an exhaustive review of the epidemiology of infant leukemia clearly distinguishing the disease from the childhood population, like many other publications, this review had no distinction for the youngest of infants in the congenital leukemia population. Ross et al. (1994) documented previous epidemiological studies in childhood leukemia, including the association with the mother's reproductive history with two or more prior miscarriages with fetal loss, OR = 1.6, 95% CI [1.0-2.7]; advanced maternal age without consistent association with elevated risk for leukemia, alcohol use during pregnancy and risk of AML under 3 years of age, OR = 3.00; AML M4/M5 under 2 years of age OR = 9.00, 95% CI [1.23-394.5]; and occupational maternal/paternal exposures were associated with an 11-fold risk for childhood leukemia in children under 6 years of age; however, these studies did not differentiate between congenital and infant leukemia.

Sande et al. (1999) conducted a general review of congenital and infant leukemia publications in order to synthesize the current medical literature documented between the diseases. All previous reports of congenital leukemia in the medical literature had focused largely on reporting single case reports that described specific presentations of the disease, including laboratory findings, treatment modalities, and outcomes. Sande et al. (1999) attributed the poor prognosis of congenital and infant leukemia to the lack of specific characteristics documented in a classification between the diseases. Sande et al. (1999) concluded that although very low numbers of congenital leukemia were present in the literature with many reports missing critical pieces of the clinical case, moving forward larger scale or multi-institutional studies were necessary to accumulate enough data to impact the diagnosis and prognosis of infants with acute leukemia.

Bresters et al. (2002) utilized data collected by the Dutch Childhood Leukaemia Study Group (DCLSG) combined with a review of English language papers on congenital leukemia or neonatal leukemia to evaluate the current medical understanding of the congenital leukemia in the Netherlands and globally from 1975 to 2000. Recognizing that infant and congenital leukemia were rare entities, Bresters et al. (2002) utilized cases reported to a centralized registry in the Netherlands, the DCLSG, which records all patients according to the classification of disease determined via bone marrow slide examination that is centrally performed and independently reviewed for diagnostic confirmation of childhood leukemia subtype (Bresters et al., 2002; Coebergh et al., 1989; M. F. Greaves & Chan, 1985).

Congenital leukemia reported in the Netherlands (15 cases) and those reported in the literature (102 cases), excluding three TMD cases, were evaluated by Bresters et al. (2002) for statistically significant differences in demographic characteristics (n = 117). Bresters et al.

(2002) reported ALL (n = 24), AML (n = 73), acute undefined leukemia (AUL; n = 6), biphenotypic/switch (now defined as MPAL; n = 8), and CML (n = 3) in the medical literature and submitted to DCLSG. The diagnostic criteria used by Bresters et al. (2002) limited the age of congenital leukemia presentation to within the first 4 weeks of life instead of the many other ranges reported in the literature.

In the group evaluated, AML was significantly more likely to be the diagnosed form of leukemia ($p < .0001$; Bresters et al., 2002). Early literature about acute leukemia in infants supported the hypothesis that males rather than females were more likely to be diagnosed. However, Bresters et al. (2002) reported there was not a statistically significant difference between the sexes ($p = .18$, females 43.6% vs. males 56.4%). Bresters et al. (2002) evaluated clinical characteristics of infants with congenital ALL and AML by FAB classification. The majority of ALL were pro-B cell (72.2%) and AML were monoblastic leukemia or M5 (58.8%), or biphenotypic/switch (now termed as MPAL; 7%), yet nearly 30.1% were unknown classification by morphological evaluation.

The cytogenetics of congenital leukemia were also evaluated by Bresters et al. (2002) with 11q23 *KMT2A*(MLL) abnormalities found in 19.4%, divided only into three types of t(v;11q23), including t(4;11) at 6.9%, t(9;11) at 2.8%, and t(11;19) at 9.7%. The remaining patients were divided into an "other" category (11.1%) or no abnormality found (27.8%). These findings form the basis for the investigation of additional abnormalities in this population in this dissertation study that may be present for further classification of the congenital leukemia as Bresters et al. (2002) suggested these findings were very diverse and, therefore, not detailed further in their study (Bresters et al., 2002). Of note, Bresters et al. (2002) reported the

congenital leukemia population was absent of all favorable cytogenetic markers typically observed in older children, including t(8;21), t(15;17), inv(16) in AML or the t(12;21) in ALL.

The therapy status of congenital leukemia patients was evaluated by Bresters et al. (2002) with only 64 patients reporting the use of chemotherapies with 20 patients dying prior to the initiation of treatment, and 26 patients electing supportive care only. In review of the patients reported only in the Netherlands, nine of 15 initiated chemotherapy with the intention to cure; however, only two survived with both requiring additional support, including post-relapse chemotherapy and bone marrow transplantation (Bresters et al., 2002). Bresters et al. (2002) performed Kaplan-Meier analysis for overall survival using time from diagnosis to death for the congenital leukemia group and OS was reported at only 31.6 ± 6.5% and the complete remission rate of 62.5%, which confirmed that patients with congenital leukemia have a poor prognosis and targeted therapies are necessary to achieve higher rates of sustained remission in this population.

Isaacs (2003) reviewed 145 cases of congenital leukemia using a Medline search of articles from 1970 to 2003 using the search terms fetal leukemia, neonatal leukemia, congenital leukemia, and infant leukemia in attempt to document the biological and clinical characteristics of the disease from that in older children. Isaacs (2003) noted that issues related to appropriate documentation of congenital leukemia are rooted in the lack of differentiation between the varied terms neonatal, infant, and congenital due to the confusion in the literature regarding the need or lack thereof to differentiate between the disease in different age groups (Isaacs, 2003).

Isaacs (2003) evaluated clinical characteristics of infants with congenital ALL and AML by FAB classification. The majority of ALL were pre-B cell and AML were myelomonoblastic/myelomonocytic (M4; 16.9%), monoblastic/monocytic leukemia (M5; 41.6%) or megakaryocytic (M7; 18.2%), yet nearly 41.2% were unknown classification by

morphological evaluation. Issacs (2003) reported nine cases of biphenotypic leukemia (now known as mixed phenotype acute leukemia; Isaacs, 2003). The cytogenetics were also evaluated with 11q23 *KMT2A*(MLL) abnormalities found in 37%, divided only into three types of t(v;11q23), including t(4;11) at (10.0%), t(9;11) at (6.0%), and t(11;19) at (15.0%; Isaacs, 2003). The remaining patients were divided into an "other" category (6.0%), t(1;22)(p13q13) (7.0%), other cytogenetic abnormality (6.0%), or no abnormality found (26.0%); additionally, children with Down syndrome were not excluded from this review of the literature, and 9% of the cases of congenital leukemia co-occurred with trisomy 21 (Isaacs, 2003). These pathologic findings of Isaacs (2003) were consistent to those of Bresters et al. (2002) in that numerous undocumented molecular, pathologic and epidemiological differences in this population may be present and may be used for further classification of the disease population. Isaacs (2003) suggested that cases in the infant population be classified as congenital if they occur within the first month of life, but that a reasonable assumption can be made that these cancers found within one year of life or later could still be deemed a congenital form of leukemia with evidence of early development (Isaacs, 2003). However, Isaacs (2003) suggested that neonatal leukemia occurring in children under 3 months of age may also be distinct from congenital and infant leukemia in older children. Isaacs (2003) stated that several leukemia studies, which included patients from birth to 18 months or 24 months of age, failed to focus on differences in children based on their age, which interfered with the appropriate classification of acute leukemia in the infant population. Therapy status of congenital leukemia patients was evaluated with 96 (66%) of patients reporting the use of chemotherapies, and only 21% of those using chemotherapy in the neonatal period surviving the disease (Isaacs, 2003). In review of the patients reported by OS, 26% of all patients with congenital leukemia survived with dismal outcomes for congenital ALL

(9%), and the highest OS for congenital AML M5 (50%; Isaacs, 2003). Isaacs (2003) reported that following clinical remission, congenital AML cases have better outcomes than congenital ALL, suggesting that differences yet to be used in classification systems may have a strong influence on the outcome.

Case reports and multicenter reports of infant and congenital leukemia are few in the literature in recent years, owing to the rarity of diagnostic cases (Brethon et al., 2016; Cao et al., 2016; De Lorenzo et al., 2014; Ergin et al., 2015; Raj et al., 2014; Taga, Tomizawa, Takahashi, & Adachi, 2016). Cao et al. (2015) collected cases from the Mayo Clinic Cytogenetics Database from 2005 to 2015 in an attempt to document differences in these rare entities using a national reference laboratory database. Cao et al. (2015) reported 85 abnormal cases of leukemia in patients under 1 year of age, including 73 patients with infant leukemia and 12 with congenital leukemia, representing 39 I-ALL and six C-ALL and 34 I-AML and six C-AML cases. Although Cao et al. (2015) reported information regarding the clinical disease of patients with congenital and infant leukemia, they did not address other epidemiological or molecular pathology data in the cohort.

Using data collected from numerous previous studies of infant leukemia in children under 1 year of age, including both congenital and infant leukemia groups, basic information has been gathered regarding the molecular pathology epidemiology of the entire age group of children that has not been previously applied to differentiate between congenital and infant groups in a classification (Bajwa et al., 2004; Bresters et al., 2002; Brethon et al., 2016; Cao et al., 2016; De Lorenzo et al., 2014; Downing et al., 2012; Forestier, Johansson, Borgstrom, et al., 2000; Forestier, Johansson, Gustafsson, et al., 2000; Gerr et al., 2010; M. Greaves, 2002; M. F. Greaves & Chan, 1985; Heerema et al., 1999; Hilden et al., 2006; Ibagy et al., 2013; Isaacs,

2003; Loeb & Arceci, 2002; Madhusoodhan et al., 2016; Masetti et al., 2015; McNeil et al., 2002; Pui, 2012; Reaman et al., 1999; van der Linden et al., 2012; van der Linden et al., 2009).

Nearly 75% of all infant ALL cases have a pre-cursor B-cell phenotype with CD19 positivity and without CD10 expression; comparatively, a single case of T-cell ALL has been described in the literature (Heerema et al., 1999; Heim & Mitelman, 2015; Tao, Valderrama, & Kahn, 2000). The dominant cytogenetic abnormalities observed with infant ALL patients include t(4;11)(q21;q23) and t(11;19)(q23;p13), which belong to WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2017 classification "B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged" (Heerema et al., 1999; van der Linden et al., 2012; van der Linden et al., 2009). The remaining 25% of infant ALL cases have yet to be classified by WHO methodology.

In AML, infants often present with myelomonocytic or monoblastic leukemia, FAB M4 and M5 respectively, characterized by immnophenotypes with CD13, CD14, CD15, and CD33 positivity (Heim & Mitelman, 2015; Isaacs, 2003; van der Linden et al., 2012). The FAB type M7, megakaryocytic leukemia, is also reported commonly in this population (Isaacs, 2003). The dominant cytogenetic abnormalities observed in infant AML include t(11;19)(q23;p13) and t(9;11)(p21;q23), which may belong to WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 2017 classifications acute myelomonocytic leukemia (AMMoL), or acute monoblastic and monocytic leukemia (AMoL); only "AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL)" is described as a recurrent cytogenetic abnormality with a distinct subtype in the classification (van der Linden et al., 2012). AMMoL and AMoL are reported in 20% and 50% of infant AML cases, respectively; the remaining 30% of infant AML has yet to be classified by WHO methodology without distinction for congenital cases from all children under 1 year (van

der Linden et al., 2012). AMMoL may involve the classification "AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1,*" "AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11,*" a translocation of 11q23 (*KMT2A*) or t(v;11q23) that may be classified as the *"*AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL)" subtype or remain as acute myelomonocytic leukemia without an associated cytogenetic aberration, which is currently recognized by the WHO classification (Van der Linden et al., 2012). AMOL may involve the classification "AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*," a translocation of 11q23 (*KMT2A*) or t(v;11q23) that may be classified as the *"*AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL)" or remain as *a*cute monoblastic and monocytic leukemia (Van der Linden et al., 2012). In infants presenting with acute megakaryoblastic leukemia (AMKL), the classification "AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*" dominates and no other cytogenetic abnormality has currently been recurrently associated with this disease entity (Van der Linden et al., 2012). Nearly 15% of infant leukemia is consistent with a complex karyotype, the presence of three or more aberrations following genetic evaluation; however, this finding was confirmed in children under 2 years (Van der Linden et al., 2012).

Early reports of congenital and infant leukemia documented cases with lymphoid and myeloid markers at presentation or at relapse termed biphenotypic/switch (Bresters et al., 2002; Isaacs, 2003). Following relapse of ALL and in ALL in the infants under 1 year of age, phenotypic switch from lymphoid to myeloid lineage (and vice versa) has been described in numerous cases with dismal outcomes for these children (Brissette, Simurdak, Larsen, & Hodges, 1996; McCoy & Overton, 1995). MPAL is currently divided into five classifications in the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 2017. The first two "mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2); *BCR-ABL1*," and "mixed

phenotype acute leukemia with t(v;11q23.3); *KMT2A* rearranged" are associated with specific cytogenetic abnormalities, whereas the remaining mixed phenotype acute leukemia with B/myeloid, NOS (no other symptoms), mixed phenotype acute leukemia with T/myeloid, NOS, and mixed phenotype acute leukemia, NOS, rare types have yet to be classified by WHO methodology (Swerdlow et al., 2017; Swerdlow et al., 2008).

Epidemiology of Congenital and Infant Leukemia

Few researchers have specifically examined race and/or ethnicity and the risk associated with the development of childhood leukemia, but rather have focused on other environmental factors that might contribute to incidence differences (Ross et al., 1994; Slusky et al., 2012). The risk for ALL is higher in developed and industrialized countries with highest incidence of ALL reported in the United States, Switzerland, and Costa Rica (Redaelli, Laskin, Stephens, Botteman, & Pashos, 2005; Robison, Buckley, & Bunin, 1995). Within the United States, the highest incidence rates for ALL have been reported in Hispanics living in the Los Angeles metro area (Redaelli et al., 2005). Caucasian infants have a higher reported age adjusted incidence of ALL in the United States at 1.5 per 100,000 and 0.9 for African American infants as reported in the year 2000 (Redaelli et al., 2005). Comparatively, African-American race has been strongly associated with a decreased risk of leukemia, and this finding has been replicated in populations around the world (Macdougall, Jankowitz, Cohn, & Bernstein, 1986; Oksuzyan et al., 2015; Redaelli et al., 2005). Oksuzyan et al. (2015) reported data from the California Cancer Registry linked to the California Birth Registry to compare 6,645 childhood leukemia cases with age related controls with a peak age of ALL documented at 2 to 5 years, and birth to 2 years for AML. Oksuzyan et al. (2015) had finding that were representative of numerous investigations of childhood leukemia with a focus on the common populations with no investigation of differences

between the youngest of children. However, Oksuzyan et al. (2015) confirmed that ethnic and racial differences are associated with the differing incidence of childhood leukemia, a finding that suggests epidemiological differences, including genetics, pathology, and demographics, may facilitate development of the disease and may be found between lineage-age stratified populations in further research.

Although a slightly higher incidence for childhood leukemia in females rather than males has been reported as similar to that in adults, there are conflicting reports of higher incidence between the sexes for ALL and AML in the infant population (Bresters et al., 2002; Isaacs, 2003; Redaelli et al., 2005). Numerous researchers of childhood leukemia report a higher incidence in males rather than females. However, the significance of this difference varies between childhood groups evaluated (Bresters et al., 2002; Isaacs, 2003; Pui, 2012).

Risk stratification. The combination of morphology, immunophenotyping, and cytogenetics is commonly used to risk stratify childhood ALL and AML (Pui, 2012). In ALL, the classification B-lymphoblastic and leukemia/lymphoma with hyperdiploidy is characterized by cases with a chromosome number greater than 50, and "B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*" classified as low risk, given their good prognoses (Emadi & Karp (2018). However, the common abnormalities of ALL in infants under 1 year, including B-lymphoblastic and leukemia/lymphoma with hypodiploidy is characterized by cases with a chromosome number less than 44, and "B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged," and "B-lymphoblastic and leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1*," are classified as high risk, given their adverse prognoses (Emadi & Karp, 2018). Patients who do not classify into either of these

risk categories, given the lack of classification category, using documented recurrent genetic abnormalities, are by default classified as intermediate risk (Emadi & Karp, 2018).

The pathology and outcomes of congenital- and infant-ALL is distinct from leukemia in older children (Bresters et al., 2002; De Lorenzo et al., 2014; Isaacs, 2003; Sande et al., 1999). Yet, the data available in medical literature regarding leukemia in children has not been consistently differentiated between children from birth to 1 year of age, often encompassing both C-ALL, and I-ALL patients into a merged I-ALL group. The merged I-ALL group may include children from birth to 1 year, birth to 18 months, or birth to 2 years of age, which has made it difficult to reveal classification differences between congenital and infant leukemia.

However, it is recognized that *KMT2A*(MLL) gene rearrangements t(v;11q23) occur at a high frequency with heterogeneous clinical outcomes in the infant population, but the partner genes for these abnormalities have not been added to the classification as distinct clinical entities (De Lorenzo et al., 2014). Previous researchers have divided I-ALL children into rearranged *KMT2A*(MLL) (*MLL*-R) and those without rearrangements (*MLL*-G), and there remains no further delineation of additional genetic aberrations that may contribute to disease burden (De Lorenzo et al., 2014). Recent studies indicate the clinical outcome of *MLL*-R and *MLL*-G patients is significantly different with *MLL*-G patients having a better event-free survival clinical outcome (De Lorenzo et al., 2014; Guest & Stam, 2017). The unique clinical outcome for *MLL*-R, and *MLL*-G has been evaluated, but no researchers have further divided the molecular pathology epidemiological data among C-ALL and I-ALL patients (Cao et al., 2016; De Lorenzo et al., 2014; Guest & Stam, 2017).

Unlike the disease in older children, children younger than 1 year with ALL are considered to have considerably higher risk, similar to all other children who present with other

high-risk characteristics of disease, including (a) a white blood cell count greater than 50,000/μL, (b) metastatic disease, and (c) poor response to treatment as determined by measurable (minimal) residual disease (MRD) after first treatment (Guest & Stam, 2017). Outcomes are poor for infant patients with ALL as the event-free survival rates range between 30% to 40%, even after intensive therapy and homologous stem cell transplantation (Bresters et al., 2002; Heerema et al., 1999).

Multiple risk classification systems exist for childhood leukemia, but they do not specifically report on age as it relates to the finding of specific genetic subtypes; instead, they were formed based on the cytogenetic findings and five-year overall survival probability (5OS) for patients in these broad childhood age groups (Chiaretti, Zini, & Bassan, 2014; Hilden et al., 2006). The United Kingdom (U.K.) Medical Research Council/United States U.S. Eastern Cooperative Oncology Group (MRC-ECOG) classified childhood ALL (excluding patients with "t(9;22)") into favorable (5OS = 0.53-0.65), intermediate (5OS = 0.41-0.48), high (5OS = 0.32-0.39), and very high risk prognostic groups (5OS = 0.13-0.28; Chiaretti et al., 2014). Comparatively, the U.S. Southwest Oncology Group (SWOG) classified childhood ALL into only favorable/intermediate (5OS = 0.52), high (5OS = 0.47), and very high risk (5OS = 0.22) prognostic groups (Chiaretti et al., 2014).

In AML, the classification "AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*," and "AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*" are classified as low risk given their good prognoses (Guest et al., 2017; Guest & Stam, 2017). Other abnormalities of AML, including monosomy of chromosomes 5 or 7, which is the case with a single chromosome 5 or 7 loss, and del(5q), which occurs when chromosome 5 has lost regions of the long (q) arm,

are classified as high risk, given their adverse prognoses (Guest et al., 2017; Guest & Stam, 2017).

Patients who do not classify into either of these risk categories, given the lack of classification category using documented recurrent genetic abnormalities, are by default classified as intermediate risk (Guest et al., 2017; Guest & Stam, 2017). Yet, the previously mentioned risk classifications include all ages of children with leukemia, not the C-AML and I-AML population (Guest et al., 2017; Guest & Stam, 2017).

The pathology and outcome of C-AML and I-AML is distinct from AML in older children (Cao et al., 2016; De Lorenzo et al., 2014). Yet, the data available in medical literature regarding leukemia in children has not consistently differentiated between children from birth to 1 year of age, often encompassing both C-AML and I-AML patients into a merged I-AML group. The merged I-AML group may include children from birth to 1 year, birth to 18 months or birth to 2 years of age, which has made it difficult to show classification differences between congenital and infant forms. C-AML and I-AML diagnoses are commonly divided by their AML-FAB type prior to incorporation of immunophenotyping and cytogenetic data per the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) guidelines; in many cases further classification is not possible due to a lack of sub-classification of abnormalities specific to the infant population.

From the data, researchers suggested that both C-AML and I-AML populations include *KMT2A*(MLL) gene rearrangements at high frequency with heterogeneous clinical outcomes based on the infant's age and initial response to treatment as measured by MRD have consistently emerged as critical prognostic indicators (Sung et al., 2010). Other documented recurrent genetic abnormalities include t(15;17) *PML-RARA*, the form of AML termed acute

promyelocytic leukemia (APL or APML), inv(16)(*CBFB-MYH11*), and *RUNX1* associated translocations (Cao et al., 2016; De Lorenzo et al., 2014). The overall survival for infants under 12 months has not improved at a rate similar to the outcome in children older than 1 year and remains at an estimated OS of 50% to 60% (Emadi & Karp). No researchers have further divided the molecular pathologic epidemiological data between C-ALL or C-AML and I-ALL or I-AML. This investigator documented specific genetic abnormalities in these age-lineage stratified groups.

Population registries for cancer research. Previous researchers who focused on leukemia have used population registries for cancer research, including Bresters et al. (2002) in the Netherlands, Lazarević et al. (2015) in Sweden, and Forestier, Johansson, Borgstrom, et al. (2000) for the Nordic Society of Pediatric Hematology and Oncology (NOPHO), and Bajawa, Skinner, Windebank, & Reid (2004) for the Paediatric Oncology Unit (POU) in the United Kingdom (Bajwa et al., 2004; Forestier, Johansson, Borgstrom, et al., 2000; Lazarević et al., 2015; Mejia-Arangure et al., 2016).

Although no previous researchers have used the SEER database to evaluate acute leukemia in the under 12 month infant population, specifically, cancer registries have been used extensively to document the leukemia populations across the US (Howlader et al., 2016; Oksuzyan et al., 2015). SEER pathologic and epidemiological studies are robust and have been applied to a wide range of hematological malignancies, including McNeil et al. (2002) in the evaluation of ALL diagnoses in the under 20 years of age population, Wang et al. (2016) investigated the association between pediatric age at leukemia diagnosis and survival, and Barrington-Trimis (2017) investigated trends in childhood leukemia incidence Oksuzyan et al., 2015).

Other researchers have used SEER to evaluate disease of young children, including Alfaar, Hassan, Bakry, and Qaddoumi (2017) in the evaluation of cancer and causes of death in neonates; Andreoli, Chau, Shapiro, and Leiderman (2017) in the epidemiological trends of retinoblastoma; and Bishop, McDonald, Chang, and Esiashvilli (2012) in the evaluation of incidence, survival, and radiation treatment for infant brain tumors; these researchers utilized the SEER database to evaluate unique aspects of the molecular, pathologic, and epidemiologic nature of given diseases of childhood. However, the differences in the under-1-year population between congenital and infant leukemia have not been studied using a national pathologic database, such as SEER (Cao et al., 2016).

Application of MPE to laboratory diagnostics. Ogino, Chan, Fuchs, and Giovannucci (2011) investigated the MPE of colorectal neoplasia, which linked genetic abnormalities with patient demographic information to intiate pecision medicine-based stratgies for targeted abnormality diagnostic testing, MPE-based stratification subsequenlty reduced costs based on genomic classification of the disease specific to the patient. Integration of molecular, pathologic, and epidemiological data into MPE stratified groups to address gaps in the medical literature can allow for the provision of more appropriate tests for the congenital and infant leukemia population (Ogino et al., 2016). The identification of genetic abnormalities linked with patient demographic information in acute leukemia could result in more refined targeted diagnostic testing, ultimately reducing costs and enhancing personalized diagnostics. The current diagnostic workup for patients with acute leukemia is expansive and often directed by first line tests, such as morphology and immunophenotyping; the appropriate classification of the disease as linked to patient demographic features could drive testing to generate only the most relevant laboratory medicine algorithms in genetic testing. This application of I-MPE-CER may reduce the

utilization of tests that do not provide meaningful results for patient care and enhance the utilization of tests with greatest diagnostic and prognostic value (Ogino et al. 2011; Ogino et al., 2016).

Summary of Literature

The appropriate diagnosis, classification, and assessment of leukemia during infancy has changed significantly in the last 100 years; these changes are closely linked to the advancement of laboratory medicine and pathologic technologies. Early case reports of a congenital form of infant leukemia were doubted by other clinicians, which continues to contribute to confusion in the medical literature over the provision of appropriate distinction of disease entities in younger and older infants. Advancements in medical diagnostics have led to the discovery of new subtypes of leukemia, generated new pathology observations, and led to the integration of multiple laboratory medicine disciplines into a globally accepted classification system: The WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues*. However, the current revision to the fourth edition of the WHO classification (2008) issued in 2017 lacks specific subgroups that recognize the epidemiologic, pathologic, or cytogenomic entities specific to congenital and infant leukemia.

This investigator utilized the recent medical data from infants under 1 year of age entered into the SEER database to evaluate the current classification systems of infant leukemia and to determine if additional characteristics were used for distinction between lineage-age stratified groups. This investigator built upon the classification system of leukemia that has advanced for nearly 150 years using information that has not yet been incorporated into The WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues* is currently in use in modern laboratory medicine and pathology diagnostic centers.

Chapter 3: Methodology

Introduction to the Chapter

Infant acute leukemia is a rare malignancy, described generally only in small cases series or reports, and there remains a paucity of data regarding the molecular pathology of the disease (Cao et al., 2016). The characteristics of the disease population are not incorporated into WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) classifications due to the rarity of disease, which has interfered with the effective diagnosis and management of the population. This investigator analyzed pathologic record data from the SEER database to appropriately categorize congenital and infant leukemia, using patient age, sex, ethnicity, disease subtype and classification, and other socio-economic factors though investigation of this population. To subgroup children diagnosed with congenital and infant acute leukemia, descriptive statistical research methodology was used to evaluate patient and pathology demographic data entered into the SEER database from 2008 to 2014.

This chapter outlines the methodology utilized in this dissertation study to select an infant patient cases series from the SEER registry. The research design is a retrospective case series, and in particular, descriptive statistical analysis was used. The data are pathologic records and a case series evaluation using descriptive statistical analysis, which is the methodology that best assessed the infant population, given the rarity of the disease. Data collection in this dissertation included requirements of resource, access, extraction, preparation, and processing for data analysis. Finally, the research procedures and analysis of the data sections are followed by reliability and validity, timeline, ethical considerations, and limitations of this dissertation study. The data were analyzed to evaluate the pathology-based classification of acute leukemia in the infant population.

Research Design and Methodology

Case series. A case series design to evaluate infants with leukemia was used. Case series involve an observation of a series of individuals with a specific condition or intervention to contribute to the clinical literature (Dekkers, Egger, Altman, & Vandenbroucke, 2012). Case series are prolific in the medical literature and can appropriately evaluate patients and disease (Dekkers et al., 2012). Case series are very common in the medical literature, have involved the evaluation of numerous diseases, and consist only of sample participants with a specific outcome under evaluation (Dekkers et al., 2012). To delineate the clinical presentation and disease course of the rare disease acute leukemia in infants, this dissertation study used a retrospective case series was used.

Data analysis. Anonymized patient pathology records refined and extracted from the SEER registry were analyzed in this dissertation study. Data were analyzed with IBM Statistical Package for Social Scientists (SPSS) Version 25.0. All collected variables were analyzed using the comprehensive analysis functionality of SPSS to produce frequency tables for preliminary analysis of the data collected for the dissertation study questions. Data analyses involved applied descriptive statistics for each patient and disease collected demographic variable.

Descriptive statistics. The data analysis strategy used in this dissertation study involved descriptive statistical analytics to document the distinct clinical presentation of children diagnosed with congenital and infant acute leukemia under 1 year of age. Patient and disease demographic data from SEER as directly deposited by participating hospital and clinic registry officials were used in this dissertation study. There were 325 records included in this cases series, which is consistent with the documented incidence of acute leukemia in the population.

Descriptive statistics were applied to the case series to evaluate the demographic and pathology data of patient records to document characteristics that produced subgroups and classifications of disease and the application of laboratory testing algorithms that provide specific results for genetic aberrations associated with WHO classifications and non-WHO classification groups. The data were extracted to IBM SPSS Version 25.0 prior to analysis.

Analysis included all infant acute leukemia in the case series, such as patients aged from birth to 1 year. Patients aged birth to under 2 months were designated "congenital leukemia," and those aged 2 months or more to less than 12 months were designated "infant leukemia." Descriptive statistics included calculation of central tendency and dispersion and shape of data demographics for patients and leukemia groups. Subtypes and classifications were measured for each categorical variable extracted from the pathology record. Categorical variables were compared using the chi-square test for congenital and infant leukemia. To compare distributions between the clinical presentation of children diagnosed with congenital and infant acute leukemia under 1 year of age, the chi-square test was used. A p value of less than .05 was used to indicate statistical significance between the childhood groups for categorical variables.

Study Design

A descriptive retrospective case series of acute leukemia patients who presented at a clinic or hospital within an NCI SEER geographic catchment area during a five-year period were included in this dissertation study (January 1, 2008, to 31st December 31, 2014).

Approach

The approach involved extraction of data from the SEER database to include only SEER 18 registry data for diagnoses between 2008 to 2014 for congenital and infant leukemia in children under 12 months of age at diagnosis, refined based on morphological diagnosis of

suspected WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) classification that were evaluated for patient and disease demographics in this dissertation study (see Figure 1).

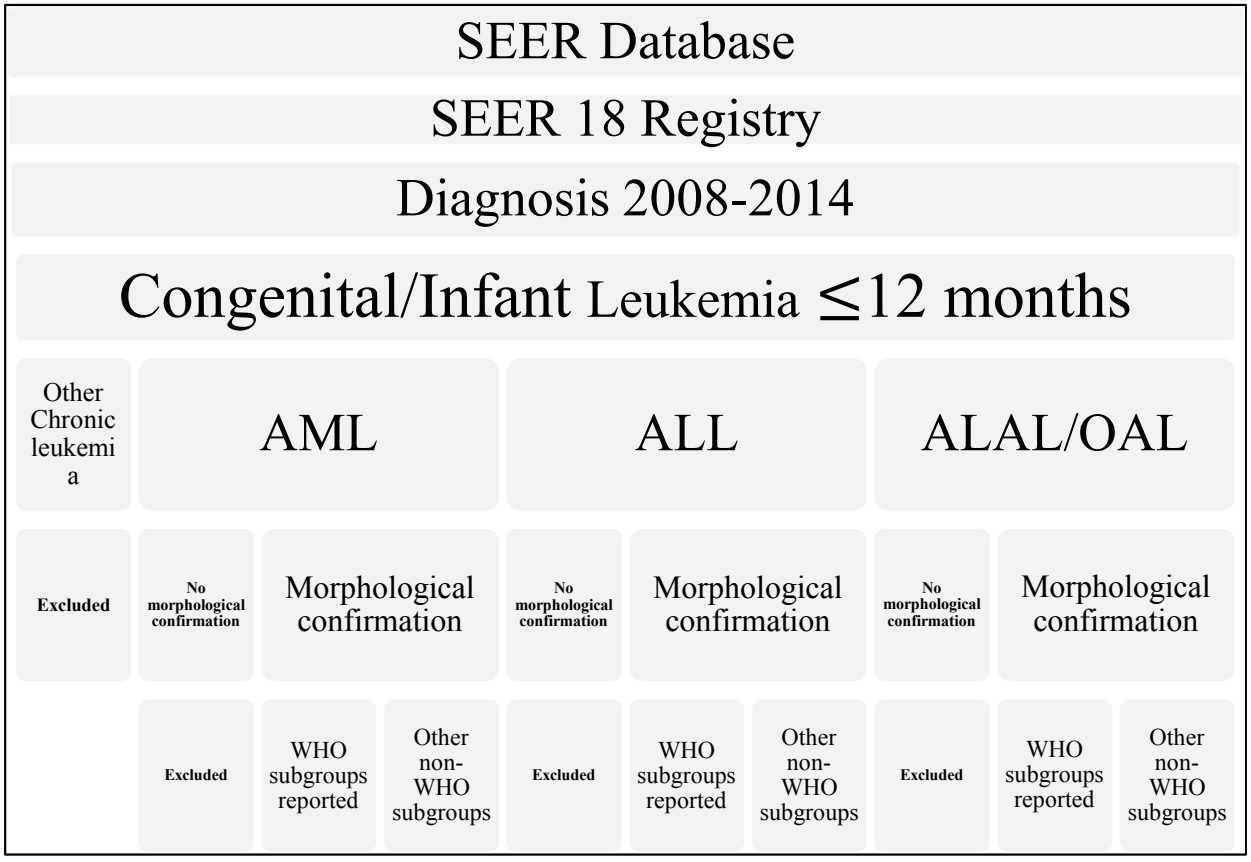


Figure 1. Dissertation study approach. Dissertation study approach of data collected from acute leukemia profiles of 325 infants under 12 months of age at diagnosis from the SEER database, 2008-2014. AML = acute myeloid leukemia. ALL = acute lymphoid leukemia. ALAL = ambiguous lineage acute leukemia. OAL = other acute leukemia.

Threats

The reliability of this dissertation study is threatened by the inherent issues related to the deposit of patient data from numerous sources to a centralized registry. The SEER cancer dataset may include errors and/or bias related to the application of health care resources, diagnosis (measurement) of the population in given areas, and the ability/inability to report all relevant clinical diagnostic information to the national registry. The inclusion of patients into the case

series in this dissertation study with only leukemia confirmed first by morphological confirmation as aligned to ICD-O-3 and WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) guidelines threatens this dissertation study. However, patients without confirmed leukemia via morphology are not likely to have subsequent diagnostic and prognostic tests for the suspected disease at that point in time; instead, they are likely to be emergent at a later period when the disease is confirmed morphologically and tested. This second clinical presentation would likely generate the primary diagnosis, which would be deposited into the SEER registry.

Additional threats to this dissertation study include the appropriate testing of queried diagnostic leukemia samples by pathology and laboratory medicine professionals. Patients should receive morphological testing via cytochemistry, immunophenotyping, cytogenetic testing, which may include karyotyping and fluorescence in situ hybridization (FISH) and molecular genetic evaluations associated with bone marrow abnormalities upon diagnosis per clinical guidelines (Creutzig, van den Heuvel-Eibrink, et al., 2012). The utilization of appropriate or inappropriate equipment/technologies maintained and validated for diagnostic use may generate bias in the diagnosis of leukemia in given areas, which may threaten conclusions drawn from evaluations of collected SEER data. Standard clinical guidelines utilized by health care professionals attempt to ensure consistency in the provision of diagnostic testing services; however, inconsistency in data generation, collection, and deposit in the SEER registry may threaten this dissertation study.

Genetic testing data are reported to be aligned with WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) guidelines in the SEER registry and patient records from cytogenetic laboratories and are reported in pathology records per the

International System for Human Cytogenomic Nomenclature (ISCN; McGowan-Jordan, Simons, & Schmid, 2016). Findings in patients records from molecular, genetic, cytogenomic, or combined cytomolecular laboratories are reported under guidance from American College of Medical Genetics and Genomics (ACMG), the Association for Molecular Pathology (AMP), and the ISCN (ISCN et al., 2016; Richards et al., 2015). However, patient records containing genetic report findings not in alignment with ACMG, AMP, or ISCN standards may bias group, subtypes, and classifications of leukemia in the case series as the registrars may be unable to appropriately code them prior to deposit into the SEER registry.

Strengths and Weaknesses of Design

Strengths of design. The research design and data collection methods are strengths of this dissertation study. The research design of a retrospective study is advantageous as these events have occurred previously, can occur in a non-controlled environment, and is relatively inexpensive relative to the likely costs associated with prospective studies. The cases series is a strength of this dissertation research design as it can provide documentation of a single group of patients with similar diagnoses, which is beneficial given acute leukemia in the infant population is a rare disease.

Weaknesses of design. The case series research design is also a weakness of this dissertation study. Cases series are extensions of single cases reports and are dependent upon the data reported within individual medical records. An additional weakness of the dissertation study design includes the identification of patient medical records from a single reporting source and the SEER registry, which may affect the accuracy and/or confound errors within records used in the dissertation study.

Specific Procedures

Data extraction. Dissertation study research access permissions were submitted to the National Cancer Institute and approval was granted prior to use of the SEER system database. Pathologic records with anonymized record numbers were extracted from the NCI SEER program database using a frequency session in SEER*Stat software version 8.3.5. Prior to data extraction, records were retrieved and viewed for SEER 18 registry acute leukemia diagnoses under 12 months of age during 2008 to 2014 within the SEER*Stat software version 8.3.5 in client-server mode. Client-server mode has a requirement for encrypted Internet access, which allows for real-time access to SEER datasets. The pathology record data included demographic and clinical data: (a) year of diagnosis (diagnosis period); (b) SEER registry data (including type of reporting clinic or hospital, registry, rural-urban location, county, state-county, and state); (c) estimated age at diagnosis; (d) sex; (e) race (ethnicity); (f) disease primary site; (g) histology and behavior;(h) diagnostic confirmation methodology (methodologies for clinical diagnostics of each test strategy); (i) ICD-O-3/WHO 2008 morphology group, subtype, and classification; (j) treatment; (k) cause of death; (l) survival months to current or COD; (m) vital status, (n) insurance status; and (o) socioeconomic variables (% of persons in county under age 18 years, % families below poverty levels, % unemployed, number of foreign born, and median household income). The pathology records of patients were exported to IBM SPSS v25.0 prior to descriptive statistical data analysis.

Case series variables.

SEER registries. The data were collected from the SEER 18 registries in SEER*Stat software version 8.3.5: Atlanta, Alaska Native Tumor Registry, Connecticut, Detroit, Greater Georgia, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Rural Georgia, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound, and

Utah (Howlader et al., 2016). Information of the reporting source and location of the registry, including county, state-county, rural or urban center, were collected. All acute leukemia cases submitted by SEER 18 registries to the centralized SEER registry that meets the inclusion criteria were analyzed in this dissertation study.

Diagnosis period. Diagnoses deposited in the SEER registry from 2008 to 2014 were evaluated in this dissertation study. The SEER 18 registry diagnostic years were refined through selection statements for year of diagnosis for pathology data in SEER*Stat software version 8.3.5. Diagnosis years 2008 to 2014 were selected by the exclusion of all other years in the registry (1973-2007). All diagnoses were categorized by their year of diagnosis into a diagnosis period.

Demographic data. Diagnoses deposited in the SEER registry from 2008 to 2014 were evaluated in this dissertation study for demographic data. The data were collected from the patients, including demographics of sex and race (ethnicity) in SEER*Stat software version 8.3.5. The sex was categorized as (male or female), race (Caucasian, African-American, Asian, Pacific Islander, Native American, or not known), and ethnicity (Hispanic or non-Hispanic).

Age at diagnosis. The SEER 18 registry was refined for children under 12 months of age at diagnosis in SEER*Stat software version 8.3.5. This refinement by age at diagnosis automatically excluded pediatric and adult forms of leukemia. Using an NCI custom data request, the age at diagnosis data in the SEER registry was made available to the primary investigator and was refined using diagnostic year and months since last birthday in SEER*Stat software version 8.3.5. Age at diagnosis for each patient was calculated as the combined month of diagnosis and year of diagnosis subtracted from combined month of birth and year of birth to produce an estimated age at diagnosis in months (designated age at diagnosis in this dissertation

study). The age at diagnosis was used in this dissertation study to document the differences of acute leukemia in congenital and infant patients within the case series.

Diagnostic confirmation methodology. The SEER 18 registry was refined in SEER*Stat software version 8.3.5 to include patients in the case series using the designated registry data codes for *Hematopoietic and Lymphoid Neoplasms* (9590/3-9992/3) provisional disease diagnostic confirmation methodologies: microscopically confirmed and not microscopically confirmed (Ruhl, Adamo, & Dickie, 2015). The microscopically confirmed category was further divided by diagnostic confirmation modality: (a) positive histology; (b) positive exfoliative cytology, no positive histology; (c) positive histology AND immunophenotyping AND/OR positive genetic studies; and (d) positive microscope confirmation, method not specified. The not microscopically confirmed category is further divided by diagnostic confirmation modality: (a) positive laboratory test/marker study, (b) direct visualization without microscopic confirmation, (c) radiology and other imaging techniques without microscopic confirmation, and (d) clinical diagnosis only. The diagnostic confirmation methodology for acute leukemia in congenital and infant patients within the case series is reported in this dissertation study to report the demographics of disease presentation and confirmation at cooperating SEER hospitals and clinics.

Primary site and morphology. The SEER 18 registry was refined in SEER*Stat software version 8.3.5 parameters to include patient records with confirmed leukemia via the International Classification of Childhood Cancer variable site code C000-C809; this step excluded records from the frequency session without data for primary site data. The acute leukemia ICCC is based on the International Classification of Diseases for Oncology (World Health Organization, 2013). The ICD-O is closely linked to the World Health Organization *Classification of Tumours of*

Haematopoietic and Lymphoid Tissues, 2008 with the ICD-O-3 aligned with the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 definitions of disease to ensure accurate diagnoses (WHO, 2013). The primary site C421 for bone marrow was used as selection statement as all hematological malignancies excluding Waldenstrom Macroglobulinemia are to be coded by registrars in this manner. The ICD-O-3/WHO 2008 recode histology types included: (a) 9800/3, (b) 9801/3, (c) 9806/3, (d) 9807/3, (e) 9808/3, (f) 9809/3, (g) 9820/3, (h) 9831/3, (i) 9833/3, (j) 9834/3, (k) 9840/3, (l) 9860/3, (m) 9861/3, (n) 9865/3, (o) 9866/3, (p) 9867/3, (q) 9869/3, (r) 9870/3, (s) 9871/3, (t) 9872/3, (u) 9873/3, (v) 9874/3, (w) 9891/3, (x) 9895/3, (y) 9896/3, (z) 9897/3, (aa) 9898, (bb) 9910/3, (cc) 9911/3, (dd) 9931/3, and (ee) 9948/3 to locate all patients who met the morphological inclusion criteria. The SEER 18 database was refined through the addition of selection statements for malignant behavior only. Using the selection criteria for site recode and ICD-O-3/WHO 2008, the sites were selected to describe the presentation of disease and tissues in acute leukemia. No patients were excluded using this applied filter as this malignancy information is linked with the provisional diagnoses as it is a criterion for acute leukemia record entry in SEER.

WHO leukemia group, subtype, classification. Refinement of the SEER data was used to generate a case series aligned the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 diagnostic criteria group, subtype, and classification. The WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 guidelines (refined in 2017) were divided hematological disorders using pathology (including genetic findings), and this classification was used to evaluate disease demographics in this dissertation study.

ALL subgroups included (a) B-lymphoblastic and leukemia/lymphoma, NOS; (b) B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities; (c) T-

lymphoblastic leukemia/lymphoma; and (d) NK cell lymphoblastic leukemia/lymphoma (Swerdlow et al., 2017). AML subtypes included (a) AML with recurrent genetic abnormalities; (b) AML with myelodysplasia-related changes; (c) therapy-related myeloid neoplasms; (d) AML, NOS; (e) myeloid sarcoma; and (f) myeloid proliferations related to Down syndrome (Arber et al., 2016; Brown, 2013; Cazzola, 2016). Acute leukemia of ambiguous lineage (ALAL) subgroups include acute undifferentiated leukemia and mixed phenotype acute leukemia (Swerdlow et al., 2017). The other acute leukemia group contains acute leukemia with little or no data regarding the clinical relevance to a single WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised in 2017) group or need for subdivision into a genetic subtype and is included in this dissertation study (Arber et al., 2016; Brown, 2013; Cazzola, 2016; Swerdlow et al., 2017).

Cytogenetic and molecular genetic data. The classification of a leukemia using WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) criteria is dependent upon the final interpretation of the case integrating genetic pathology data, such as cytogenetic, cytogenomic, and/or molecular genetic findings. The final classification or the lack thereof was a variable evaluated in the case series and included in this dissertation study. Presentation of this information can be used to provide information regarding the use of genetic pathology in the diagnosis of leukemia in the congenital and infant population.

Treatment. The case series includes data reported regarding the treatment modalities used in the management of congenital and infant leukemia. Lymphomas may be treated with surgery (extranodal or nodal), chemotherapy, and/or radiation, while leukemias are frequently treated with chemotherapy and bone marrow transplants; it was anticipated that patients would be treated with chemotherapy and/or radiation (Brown, 2013). The treatment fields included data

from (a) radiation sequence with surgery, (b) reason no cancer directed surgery, (c) radiation treatment, and (d) chemotherapy. However, the treatment fields radiation sequence with surgery and reason no cancer directed surgery were excluded as cancer directed surgery is not appropriate for hematological leukemia malignancies (Brown, 2013). Radiation treatment fields include none/unknown and beam radiation, whereas chemotherapy fields include no/unknown and yes.

Cause of death. The case series includes COD in infants diagnosed with acute leukemia. The NCI SEER registry uses the COD recode 1969+ (04/16/2012), which is aligned with the ICD-O versions 8 to 10 for years of death after 1969 as this recode has allow site-related CODs to be defined consistently over time to ensure long-term trends are reported accurately (Howlader et al., 2017). The COD recode 1969+ (04/16/2012) includes both cancer and non-cancer causes of death reported for patients in the SEER registry. The SEER registry COD recode 1969+ (04/16/2012) is aligned with ICD-10 for all deaths after 1999, and all cases analyzed in this dissertation study were aligned with this ICD code (Howlader et al., 2017). ICD-10/COD codes for cancer-related deaths in this case series include (a) ALL (C91.0), (b) other lymphocytic leukemia (C91.2-C91.4, C91.7, C91.9), (c) acute myeloid (C92.0, C92.4-C92.5, C94.0, C94.2), (d) acute monocytic leukemia (C93.0), (f) other myeloid/monocytic leukemia (C92.2-C92.3, C92.7, C92.9, C93.1-C93.2, C93.7, C93.9), (g) other acute leukemia (C94.4, C94.5, C95.0), and (h) aleukemic, subleukemic, and NOS (C90.1, C91.5, C94.1, C94.3, C94.7, C95.1, C95.2, C95.7, C95.9). Patients were also designated as “Alive” (00000); however, those with “unknown/missing/invalid COD” were entered as (99999). The cases series was evaluated for vital status of all patients diagnosed with leukemia: alive or dead. The survival status was reported for those without a COD; however, those designated alive did not have long-term

follow-up, given that those diagnosed in 2014 had at most 2 years only of survival data within the database.

COD was used to report the characteristics of acute leukemia in the years 2008 to 2014. Specifically, how COD differs in lineage-age stratified groups between this period using the vital status of patients in the case series was evaluated. COD differences were evaluated in the congenital and infant acute leukemia (AL) patients in during this period.

Socioeconomic data. The case series included data reported regarding socioeconomic status of counties in which infants diagnosed with acute leukemia reside.

Age in area. The variable "% of persons in county under age 18 years" was calculated as the percentage of persons in this age group as a proportion of individuals reported in the U.S. census 2011to 2015 data.

Poverty in area. The variable "% of families below poverty" was calculated as the percentage of families whose incomes that fall below calculated values from the U.S. census 2011to 2015 data; calculation from the U.S. census 2011 to 2015 data is a ratio of income to poverty level in the preceding 12 months of families with related children under age 18. The percentage of families below poverty was reported at 100% and 150% of poverty level respectively.

Employment in the area. Using the U.S. census 2010 to 2014 data, the employment of the population aged greater than 16 years unemployed was reported for the diagnosis area. The calculated variable "% unemployed" reports from the civilians in the labor force who are not employed; those in the armed forces and not in the labor force were not included in the calculation.

Foreign born in the area. Using the U.S. census 2010 to 2014 data, the percent of persons who were foreign born was reported for the diagnosis area. The calculated variable "% of foreign born" was derived from birth by nativity and citizenship status to designate a foreign-born individual in a given area.

Median household income. The median household income as taken from the U.S. census 2010 to 2014 data was reported. This calculated variable "*median household income*" was derived from income during the past 12 months with appropriate inflation adjustment dollars for 2014.

Insurance status. The case series included data reported regarding the insurance status of infants diagnosed with acute leukemia. The NCI SEER registry uses the "Insurance Recode (2007)+" derived from the North American Association of Central Cancer Registries (NAACCR) primary payer at diagnosis field (Howlader et al., 2017). The code insurance recode (2007)+ included (a) uninsured; (b) any Medicaid; (c) insured; (d) insured, no specifics; (e) insurance status unknown; and (f) blank(s). The uninsured category was divided into not insured and not insured, self-pay. The any Medicaid category was divided into (a) Indian/Public Health Service; (b) Medicaid; (c) Medicaid, administered through a managed care plan; and (d) Medicare with Medicaid eligibility. The insured category was divided into (a) private insurance with fee-for-service; (b) private insurance with managed care, health maintenance organization (HMO) or preferred provider organization (PPO), and TRICARE; (c) Medicare, administered through a managed care plan; (d) Medicare with private supplement; and (e) Medicare with supplement, NOS, and military. The insured, no specifics category was divided by (a) Medicare/Medicare, NOS; (b) insurance, NOS. The insurance status unknown and Blank(s) codes were not divided further.

Participants

The participants of this dissertation study included minors under age 12 months with pathologic record data transferred to the NCI SEER registry.

Power

The G*Power software version 3.1 was used to calculate power for this dissertation study. The Z Generic Z test with a proportion (difference between two independent proportions) with a priori (compute required sample size, given α, power, and effect size) was used to calculate power. A power calculation of (1-β error probability, 0.95) was used to calculate the critical Z for this dissertation study of 1.6449, α error probability .05.

Sample Size

The incidence of acute leukemia in the US is 41 cases per million infants, which equates to approximately 160 cases of infant leukemia each year (Brown, 2013). Using the incidence data, an estimated 960 cases were to be diagnosed in the US over the six-year period analyzed in this dissertation study, and the SEER registry is known to capture diagnoses for approximately 28% of the population; however, 325 records were available for this dissertation study. Exclusion criteria refinement reduced the final case series for inclusion in this case series prior to extraction from the SEER database.

Inclusion Criteria

The inclusion criteria included pathology data stored in the SEER 18 registry following diagnosis. Data were selected based on diagnoses during January 1, 2008, to December 31, 2014. Diagnoses of leukemia in children under 12 months of age were included; data may have included children stillborn or aged under birth (pre-natal diagnoses) and those aged over 12 months prior to diagnoses due to the inherit data entry process by SEER registrars that does not provide researcher access to exact date of birth to maintain privacy. Female and male sex were

included; no patients without sex information were included in the case series non-classified group. All race and ethnicities reported within the case series were included; the patients without ethnicity information were included into a non-classified/unknown group. Acute leukemia diagnoses using ICD-O-3/WHO 2008 via morphological confirmation with bone marrow infiltration were included as this tool is the primary diagnostic tool routinely used to initiate further laboratory testing.

Exclusion Criteria

The exclusion criteria included pathology data stored in the SEER 18 registry following diagnosis within the following subtypes: myeloid sarcoma, myeloid proliferations related to Down syndrome, transient abnormal myelopoiesis associated with Down syndrome, myeloid leukemia associated with Down syndrome, myeloproliferative neoplasms, mastocytosis, myelodysplastic/myeloproliferative neoplasms, myelodysplastic syndromes, and myeloid neoplasms with germline predisposition. These subgroups were excluded as the aim of this dissertation study was to evaluate acute forms of disease in the infant population. Patients diagnosed with acute leukemia not coded by SEER professionals into an ICD-O-3/WHO 2008 code were excluded.

Recruiting Procedures

Pathology records are deposited in the SEER database and did not require recruitment for this dissertation study. Data are entered into the electronic patient medical record during routine diagnosis and management of the patient at clinics and hospitals within a participating SEER registry (NCI, 2010). SEER cancer registry personnel at each participating clinic or hospital entered the data into the centralized SEER Data Management System (SEER*DMS; Howlader et al., 2016; NCI, 2010). SEER registry data are reviewed by registry officials for quality

management and population-based research activities performed at the National Institutes of Health. The SEER data are released annually following the review for research purposes. The last release of data prior to initiation of this dissertation study was April 16, 2018.

Format for Presenting Results

Variables.

SEER registries. The data collected from the SEER 18 registries were presented with reference to statistical geography aligned with boundary delineation of given registries. All 18 SEER registries (Atlanta, Alaska Native Tumor Registry, Connecticut, Detroit, Greater Georgia, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Rural Georgia, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound, and Utah) were depicted geographically to give spatial awareness to areas of diagnosis in the presentation of data. In addition, descriptive statistical data of the given SEER registry area were presented as proportions of congenital ALL, AML, ALAL, AOL, and infant ALL, AML, ALAL, OAL as related to all diagnosed acute leukemia in the under-one-year-at-diagnosis case series.

Diagnosis period. The data collected from the diagnosis period of 2008 to 2014 were presented as a table. The total diagnoses for a given year were presented alongside a percentage of all diagnoses of acute leukemia included in the case series of this dissertation study.

Demographic data. The SEER demographic profiles of the case series were presented as a table. The variables *N* (cases series number), age (mean $\pm$ *SD*), sex (male or female), and race (Caucasian, African American, Asian, Pacific Islander, and Native American) and ethnicity (Hispanic/non-Hispanic) were presented. These data were presented for the entire case series and divided into the congenital (< 2 months) and infant ($\leq$ 2-12 months) leukemia diagnostic groups based on age.

Age at diagnosis. The age at diagnosis data in the SEER registry is a calculated variable and was presented in the demographic data section as overall case series value. However, as this investigator aimed to evaluate the portion of acute leukemia linage-age stratified groups, these data were presented as a percentage of congenital versus infant leukemia in a table.

Diagnostic confirmation methodology. The diagnostic confirmation methodology used to diagnose acute leukemia were presented as a multilevel pie chart and a table. The provisional disease diagnostic confirmation methodologies microscopically confirmed and not microscopically confirmed and their respective categories form branch nodes from the root node of confirmation methodology technique.

WHO leukemia group, subtype, and classification. The leukemia diagnoses of the case series are presented as a chart between lineage of leukemia lymphoid (ALL), myeloid (AML) mixed (ALAL), or other (OAL). A single table is presented with the overall distribution as a case series percentage of WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) leukemia groups with the total *N* (case series number, %).

ALL was divided into three groups: (a) B-lymphoblastic and leukemia/lymphoma, NOS; (b) B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities; and (c) T-lymphoblastic leukemia/lymphoma; a single chart presented this group with the total *N* (case series number, %).

ALL subgroup 1 B-lymphoblastic and leukemia/lymphoma, NOS was not divided further as there are no currently defined classifications, and this subtype were presented only in the total chart of ALL group with the entire acute leukemia case series.

ALL group 2 B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities was divided by classifications (subtypes): (a) B-lymphoblastic and

leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1,* (b) B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged, (c) B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1,* (d) B-lymphoblastic and leukemia/lymphoma with hyperdiploidy, (e) B-lymphoblastic and leukemia/lymphoma with hypodiploidy, (f) B-lymphoblastic and leukemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3,* (g) B-lymphoblastic and leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1,* (h) B-lymphoblastic and leukemia/lymphoma, *BCR-ABL1-like,* and (i) B-lymphoblastic and leukemia/lymphoma with iAMP21; a single table presented these subtypes with the total *N* (case series number, %).

The ALL group 3 T-lymphoblastic leukemia/lymphoma was not divided further as there is currently only a single defined classification: early T-cell precursor lymphoblastic leukemia, and this group is presented only in the total table of ALL diagnoses with the entire acute leukemia case series.

AML was divided into three groups: (a) AML and related neoplasms; (b) acute leukemias of ambiguous lineage; and (c) aleukemic, subleukemic, and NOS; a single table presents this group with the total *N* (case series number, %).

AML group 1 AML and related neoplasms was divided by subtypes: (a) AML NOS, (b) AML with recurrent genetic abnormalities, and (c) AML with myelodysplasia related changes; a single chart presents these subtypes with the total *N* (case series number, %).

The AML NOS subtype was divided by classifications: (a) AML NOS without further stratification, (b) acute monoblastic/monocytic leukemia, (c) acute megakaryoblastic leukemia, (d) AML with minimal differentiation, (e) acute myelomonocytic leukemia, (f) AML with maturation, (g) acute panmyelosis with myelofibrosis, (h) AML without maturation, (i) pure

erythroid leukemia, and (j) acute basophilic leukemia; a single table presents these subtypes with the total *N* (case series number, %).

The AML with recurrent genetic abnormalities subgroup was divided into classifications (subtypes): (a) AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1,* (b) AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11,* (c) APL with *PML-RARA,* (d) AML with t(9;11)(p21.3;q23.3) *MLLT3-KMT2A*(MLL), (e) AML with t(6;9)(p23;q34.1); *DEK-NUP214,* (f) AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM,* (g) AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1,* (h) AML with mutated NPM1, (i) AML with biallelic mutations of *CEBPA,* and (j) provisional entities: AML with *BCR-ABL1* and AML with mutated *RUNX1*; a single table presents these subtypes with the total *N* (case series number, %).

The AML with myelodysplasia-related changes subtype was not divided further as there are no currently defined classifications and this subtype was presented only in the total table of AML and related neoplasms within the entire case series.

The AML Group 2*,* acute leukemias of ambiguous lineage, was divided by subtypes: (a) acute undifferentiated leukemia; (b) mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2); *BCR-ABL1*; (c) mixed phenotype acute leukemia with t(v;11q23.3); *KMT2A* rearranged; (d) mixed phenotype acute leukemia with B/myeloid, NOS; and (e) mixed phenotype acute leukemia with T/myeloid, NOS; a single chart presents these classifications with the total *N* (case series number, %).

The AML Group 3, aleukemic, subleukemic, and NOS was not divided further into subtypes for presentation of data as there are no currently defined classifications, and this group

was presented only in the total chart of AML diagnoses with the entire acute leukemia case series.

Each leukemia classification data was presented with the overall distribution as a case series percentage of the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) classifications with the total *N* (case series number, %) in a table. A summary of congenital and infant leukemia clinical presentations, including group, subtype, and classification overall, was presented as table summarizing the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) diagnoses.

Cytogenetic and molecular genetic data. The molecular pathology profiles of the case series were presented as a pie chart with the percentage of patients with cytogenetic, molecular, genetic, or no genetic findings. The WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 2008 (revised 2017) groups, subtypes, and classifications that require cytogenetic and molecular genetic data are the only diagnoses presented in this section, including overall distribution of each category with the total (case series number, %) in a table and figure.

The SEER genetic profiles as characterized in pathology reports are presented as a table. The molecular pathology profiles are matched to the respective ICD-O-3/WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) and are presented with the overall distribution as a case series percentage of the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) classifications with the total *N* (case series number, %) in a chart.

Treatment. The treatment of leukemia diagnoses of the case series was presented as a pie chart, including surgery (extranodal or nodal), chemotherapy, and radiation. A single table is

presented with the overall distribution as a case series percentage between lineage stratified groups with the total *N* (case series number, %) of acute leukemia.

The treatment Group 1, surgery (extranodal or nodal), was not presented as it is not appropriate for hematological leukemia malignancies. The treatment Group 2, chemotherapy, was divided by whether the group presented no/unknown or yes; a single chart presents chemotherapy treatment with the total *N* (case series number, %). The treatment Group 3, radiation, was divided by whether the group presented no/unknown or beam radiation; a single chart presents radiotherapy treatment with the total *N* (case series number, %). Additionally, the proportion of each treatment or lack thereof was presented for congenital and infant AL in a table.

Cause of death. The cause of death following leukemia diagnoses of the case series were presented as a pie chart: cancer or non-cancer. A single table is presented with the overall distribution as a case series percentage. The case series was divided by vital status alive or dead; a single table presents this status with the total *N* (case series number, %).

The cancer group was divided by cancer-related deaths in this case series, including (a) ALL (C91.0); (b) other lymphocytic leukemia (C91.2-C91.4, C91.7, C91.9); (c) acute myeloid (C92.0, C92.4-C92.5, C94.0, C94.2); (d) acute monocytic leukemia (C93.0); (e) other myeloid/monocytic leukemia (C92.2-C92.3, C92.7, C92.9, C93.1-C93.2, C93.7, C93.9); (f) other acute leukemia (C94.4, C94.5, C95.0); and (g) aleukemic, subleukemic, and NOS (C90.1, C91.5, C94.1, C94.3, C94.7, C95.1, C95.2, C95.7, C95.9 or as consistent with cancer diagnosis); a single figure presents cancer causes of death with the total *N* (case series number, %). The CODs are presented for the lineage-age stratified groups and in a single table.

Socioeconomic data. The socioeconomic data of the registry areas with leukemia diagnoses were presented as separate tables. All areas have data presented for calculation of children in the area % of persons in county under age 18 years, poverty of the area % of families below poverty, employment of the area, foreign born of the area, and median household income of the area. The insurance status of the case series was presented as a table, first as insured and uninsured subsequently divided by types of coverage.

Resource Requirement

The resources that were required for this dissertation study were minimal. A computer equipped with or capable of running a Windows-based operating system, Internet access, and SEER*Stat software version 8.3.5 were required to retrieve SEER data. NCI SEER makes no recommendation about the specific computational power of the computer hardware system for retrieval and manipulation of SEER data (Murphy, Alavi, & Maykel, 2013). To evaluate and analyze the retrieved SEER data, IBM SPSS version 25.0 was required. The principal investigator received the required approved researcher access to the NCI SEER database with custom data requests for the database specific fields: Incidence SEER 18 custom data with months since last birthday and additional treatment fields, November 2016 release (1973-2014).

Reliability and Validity

Reliability. Following the unification of cancer registries across the US into the NCI SEER program in early 1970 to 1973, the use of the SEER database in research to evaluate characteristics of a given cancer population has increased exponentially (Lau, Mahendraraj, Ward, & Chamberlain, 2016; McNeil et al., 2002). The medical record data collected and accessible via the NCI SEER program is a reliable tool routinely used to research and refine the classification of disease (Duggan et al., 2016; Lau, Mahendraraj, & Chamberlain, 2015; National

Cancer Institute, 2010; Printz, 2015). Using the SEER registry, previous researchers have studied numerous demographic populations to evaluate disease incidence, presentation, treatment, and outcomes patient populations (Alfaar et al., 2017; Bishop et al., 2012; Lau et al., 2015; McNeil et al., 2002). The accuracy and reproducibility of pathology diagnoses using internationally acceptable guides, such as the WHO, have been enhanced from research studies using SEER registry data through the integration of complex diagnostic data with patient demographics (Duggan et al., 2016).

Validity. The use of population demographic data in this dissertation study is a valid tool, given the assumption that single patient pathology record data can be grouped by their common diagnoses and evaluated simultaneously (Bray & Parkin, 2009; Dubecz et al., 2012). Descriptive statistical analysis is valid tool for evaluation of data in this dissertation study as it can be used to document the demographics of the congenital and infant acute leukemia population in children under 1 year of age. Conclusions drawn from statistical evaluations performed in this dissertation study are valid given the assumption characteristics of the population, including preliminary diagnoses, laboratory workup, test sensitivities, and diagnoses, are correct in the pathology record within the SEER database.

Secondary data validity. The NCI SEER database is the source of data in this dissertation study, and the validity of secondary data sources is directly linked to the source of the data. The SEER program is a global exemplar for quality in cancer registry standards (National Cancer Institute, 2010). The NCI SEER database is held to the highest of quality standards as it is routinely evaluated via Web-based reliability studies to ensure data quality accuracy; an assurance program is in place for all errors detected in an attempt to enhance improvement processes (NCI, 2010). The skills of SEER registry personnel and measures consistency in

medical record coding within data held within the dataset and newly coded data is regularly evaluated by using the SEER quality accuracy and assurance program (NCI, 2010). This review process is used to ensure patient medical record data are collected from all cancer diagnoses within registry-designated clinics and hospital sites and that the data are collected in a reliable and valid standard operating procedure to include all pathology data that may occur during the disease course and management (NCI, 2010).

Internal validity. Internal validity of the findings of this dissertation study include inherent selection bias within the SEER program. Specifically, not all cancer diagnoses in the US use the same diagnostic algorithms prior to entering data into the SEER registry. Additionally, as access to care may prohibit patients from seeking all diagnostic testing and management, the socioeconomic status of children was collected in this dissertation study. The collection of this data documents whether there may an inherit exclusion of diagnoses otherwise representative of congenital and infant leukemia given this access to care concern. These data are a threat to internal validity as this investigator aimed to accurately describe the relationship between demographics of children with acute leukemia under 1 year of age.

External validity. External validity of the findings of this dissertation study include the limited regions of the US childhood leukemia population represented by a SEER registry. The case series for this dissertation study include children with congenital and infant acute leukemia in the SEER registry regions. However, the demographic and pathology findings are generalizable to all children with morphologically confirmed acute leukemia diagnosed under 1 year of age across the globe.

Timeline

The principal investigator of this dissertation study submitted an NCI SEER research data agreement on February 1, 2017 and was subsequently granted access to SEER data on February 3, 2017, which remained active for use in this dissertation study. Access to data used in this dissertation study is granted to all general SEER users following a research data agreement; however, a custom data request was required for access to the radiation/chemotherapy (treatment) database and months since last birthday for children diagnosed during 2008 to 2014. These data can be viewed by all users with a research data agreement; however, the data were not manipulated prior to ethical approval. Data collection commenced immediately following the Nova Southeastern University (NSU) Institutional Review Board (IRB) approval received on May 14, 2018, on a single date from the SEER database: May 15, 2018. A 1.5-month period was required for data analysis and was followed by 1.5 months for data interpretation. This dissertation study was completed on August 3, 2018.

Ethical Considerations and Review

The NSU IRB requests for dissertation study approval were submitted on April 28, 2018. The NSU IRB approval date was received May 14, 2018, with IRB number 2018-259, titled The Integrative Molecular Pathological Epidemiology of Congenital and Infant Acute Leukemia. The dissertation study was deemed exempt from further review under 45 CFR 46. 101(b) (Exempt Category 4).

This investigator utilized data from the NCI SEER cancer registry that is de-identified from pathology reports and anonymized prior to public release. The Health Insurance Portability and Accountability Act (HIPAA) requires researchers using personal identification with medical data to protect human subjects to decrease risks of infringing on individual rights (McLaughlin et al., 2010). Personal identifying health data are captured by SEER in many instances via statutory

mandates in each state rather than by voluntary processes, requiring informed consent agreements with individual patients and/or their families (McLaughlin et al., 2010).

Individual SEER registries along with their associated hospitals and clinics may apply HIPPA to regulate their release of data to the NCI (McLaughlin et al., 2010). As each SEER registry's standard operating procedure may deviate in the application of HIPAA to cancer registry data, and the requirements or the lack thereof for consent of SEER data entry and consent for entry of childhood medical records may have been obtained from parents with and without English speaking skills (Herdman et al., 2006; Nass et al., 2009). Risk to individual rights is minimized with the use of SEER data as it is anonymized prior to release for research, such as that performed in this dissertation study.

The SEER Cancer Statistics Review (CSR) 1975 to 2014 as published by the NCI's Surveillance Research Program (SRP) was released on April 14, 2017. The release of the NCI SRP CSR places the material within the report into the public domain that can be reproduced or copied without permission (Howlader et al., 2016; Howlader et al., 2017). The NCI SEER program was established in 1973; however, congressional action in 1992 made the transfer of cancer data to the registry a legal requirement (McLaughlin et al., 2010).

Funding

This dissertation study was unfunded.

Study Setting

The investigator utilized data collected from the SEER 18 registry. The data were retrieved from the NCI (SEER) database (https://seer.cancer.gov/data/) The medical record data were accessed from servers located at

BG 9609 MSC 9760

9609 Medical Center Drive

Bethesda, MD, USA 20892-9760

All retrieved and analyzed data will be stored on the encrypted hard drive of the principal investigator for 3 years following conclusion of this dissertation study.

Instruments and Measures

The instruments used in this dissertation study were minimal, including a basic computer equipment and software. The utilization of descriptive statistical studies as the measurement tool in this dissertation study is most appropriate given the aim is to describe the phenomena of acute leukemia diagnosis in infants under 12 months of age without making claims regarding association nor causation of the disease. Descriptive statistics are reliable and valid measurement tools that report on central tendency, dispersion, and shape data derived from a variable.

Pilot Study Summary

A pilot study examined a cases series of congenital and infant AML pathology records from the NCI SEER registry to define the patient and molecular pathology disease demographic factors unique to children under 12 months of age at diagnosis (H. Williams, 2017). The pilot study retrieved demographic and clinical data for a case series of 105 congenital and infant AML from the SEER database for the years 2010-2013 (H. Williams, 2017). This pilot study confirmed data collected from the SEER registry is appropriate to evaluate the infant population to describe characteristics of leukemia (H. Williams, 2017). The pilot study confirmed pathology demographic data can be evaluated using the SEER registry (H. Williams, 2017).

Data Collection Procedures

Data for this dissertation study was extracted from the SEER 18 registry database; no primary data collection occurred. Data were retrieved from SEER pathology records for children under 1 year of age diagnosed with acute leukemia form 2008-2014. As pathology record data within the SEER data is anonymized, no identifiable information was stored from case series patients collected from SEER and the participating registries. The PI did not have access to identifiable patient data and as such it will never be shared from this dissertation study. Regardless of previous anonymization by SEER, all pathology record data were accessed via the secure SEER* Stat client mode.

Data Analyses

The utilization of a descriptive statistical analysis for this dissertation study is appropriate as the study sought to describe the diagnosis of acute leukemia in the under 1 year of age population without an evaluation of association or causation between factors observed.

Following extraction of data from the SEER registry using the SEER*Stat software, data extracted to SPSS was stored and will be stored for 36 months after the conclusion of this dissertation study on an encrypted start up disk secured with a password known only to the primary investigator of this dissertation study. The data were collected on a single date, May 15th, 2018, which followed Nova Southeastern University Institutional Review board approval, from the SEER*Stat software. The SEER*Stat software server located in Bethesda, MD, USA was accessed from a secure internet connection based in London, UK. The data were moved immediately to SPSS, where it was evaluated over 1.5 months of data analytics. All evaluation of the data occurred on the specified encrypted and password protected computer of the primary investigator of this dissertation study. Data were transmitted subsequently in an anonymized and accumulated manner for the report of this dissertation study.

Data collected were analyzed using the SPSS version 25.0. Analysis for all variables was conducted in the comprehensive analysis functionality of SPSS with frequency tables being populated for all variables to gain better insight into the results of data collection. Correlation matrices were created for all demographic variables against each other in order to determine any significant *p* values. Descriptive statistics such as mean and median, standard deviation were calculated for each variable and any relationships that emerged were assessed. The Chi-square test was used to evaluate the null hypotheses of this dissertation study. The null hypothesis H_0 was that the demographics of children with leukemia diagnoses under 2 months of age (congenital) will be significantly (*0.05*) different from those of older infants over 2 months of age (infant).

Research question 1 "What is the distinctive clinical presentation of children diagnosed with congenital and infant AML and ALL under 1 year of age in the SEER database between 2008-2014 in the United States?" was answered with descriptive statistics including mean, median, and standard deviation calculated for each variable and presented for AML, ALL, ALAL, and OAL.

Research question 1.1 "Are there distinctive clinical presentations of children diagnosed with congenital AML and ALL at 1 and 2 months of age?" was answered with descriptive statistics including mean, median, and standard deviation calculated for each disease pathology variable and presented for both AML and ALL. The records were divided by disease ALL or AML, ALAL, OAL and at ages birth to less than 1 month, and greater than or equal to 1 to less than 2 months. The Chi-square test was used to evaluate the differences between the lineage and age groups; the null hypothesis of the test was that the age of diagnosis would not be significantly related to the type of leukemia diagnosed.

Research question 2 “What is the epidemiological profile of cases of congenital and infant leukemia AML and ALL in the SEER database between 2008-2014 in the United States?” was answered with descriptive statistics including mean, median, and standard deviation calculated for each demographic variable and presented for AML, ALL, ALAL, and OAL. The records were divided by disease lineage, and age stratification from birth to under 1 year. The Chi-square test was used to evaluate the differences between the disease and age groups; the null hypothesis of the test was that the age of diagnosis would not be significantly related to WHO subtype of leukemia.

Research question 2.1 “What is the proportion of congenital AML and ALL in 1 to 2-month-old infants?” was answered with descriptive statistics including a table comparison of the reported cases within each disease group. The Chi-square test was used to evaluate the differences between the disease and age groups.

Research question 2.2 “What is the proportion of infant AML and ALL in 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12-month-old infants” was answered with descriptive statistics including a table comparison of the reported cases within each disease group. The Chi-square test was used to evaluate the differences between the disease and age groups; the null hypothesis of the test was that the age of diagnosis would not be significantly related to proportion of leukemia diagnosed by each lineage type.

Research question 2.3 “What is the proportion by sex of congenital AML, congenital ALL, infant AML, and infant ALL?” was answered with descriptive statistics including a table comparison of the reported cases within each disease and age group. The Chi-square test was used to evaluate the differences between the disease and sex groups; the null hypothesis of the test was that the sex of record would not be significantly related to leukemia group diagnosed.

Research question 2.4 “What is the proportion by SEER registry region of congenital AML, congenital ALL, infant AML, and infant ALL?” was answered with descriptive statistics including a table comparison of the reported cases within each disease and age group within the registry area. The Chi-square test was used to evaluate the differences between the registry groups; the null hypothesis of the test was that the registry group would not be significantly related to leukemia group diagnosed.

Research question 2.4.1 “What are the characteristics of the highest proportion SEER registry region counties (where diagnosed) by families below poverty, families below 150% of poverty in county, number unemployed in county, median family income, and number of foreign born individuals?” was answered with descriptive statistics including a table comparison of the reported case characteristics within the top 20% of all registry areas.

Research question 2.5 “What is the cause of death proportion by congenital AML, congenital ALL, infant AML, and infant ALL?” was answered with descriptive statistics including a table comparison of the reported cases within each disease and age group. The Chi-square test was used to evaluate the differences between the disease and age groups; the null hypothesis of the test was that the cause of death would not be significantly related to leukemia group diagnosed.

Research question 3 “How do the characteristics of AML and ALL differ, addressing differences in mortality over time between 2008-2014 in the United States” was answered with descriptive statistics including deaths reported and mean values calculated for each year and presented for both AML, ALL, ALAL, and OAL.

Research question 3.1 “How do the mortality rates among congenital AML, congenital ALL, infant AML, and infant ALL differ during this period?” was answered with descriptive

statistics including deaths reported and mean values calculated for each year and presented for both congenital and infant acute leukemia. The Chi-square test was used to evaluate the differences between the disease and age groups by deaths; the null hypothesis of the test was that the mortality rates would be significantly related to leukemia group diagnosed.

Research question 3.2 “What are the differences in treatment administered among congenital AML, congenital ALL, infant AML, and infant ALL during this period?” was answered with descriptive statistics including treatments reported and mean values calculated and presented for both congenital and infant acute leukemia. The Chi-square test was used to evaluate the differences between the disease and age groups by treatment administered; the null hypothesis of the test is that the treatment administered would not be significantly related to leukemia group diagnosed.

Summary of the Chapter

There is currently a dearth of pathology and demographic data available regarding congenital and infant acute leukemia, and differences in presentation between the two populations based on the age of the child. The NCI SEER database, a population cancer registry, has been extensively used in health science research to evaluate cancer diagnosis, management, and outcomes since 1973, however it has not been previously used to document specific subgroups of children with congenital and infant leukemia. Using a retrospective case series evaluated with descriptive statistics this dissertation study aimed to document additional patient and pathology demographic data. This dissertation study used medical record data previously collected by health care professionals that was readily access for research purposes with few resource requirements. Documentation of patient demographics can assist in the development and revision of WHO guidelines for acute leukemia diagnoses in the infant population.

Chapter 4: Results

Introduction to the Chapter

This study is rooted in the lack of further classification of rare acute infant leukemia in children under 12 months of age and adds to our understanding of the disease course from presentation until remission or death. There is extensive literature about leukemia in children, but the evaluations are dominated by children 12 months of age or older. There remain few pieces of extensive literature about this population to assist in the understanding of the disease. The most recent large-scale study based on a freely accessible population database occurred in the Netherlands in 2002 with data from the Dutch Childhood Leukaemia Study Group (DCLSG); other U.S.-based studies have been completed by the Children's Oncology Group clinical trials member institutions through National Cancer Institute funded studies. There have been no previous studies of congenital and infant leukemia pathology and demographics using the U.S. SEER registry. The purpose of this dissertation study was to generate a detailed evaluation of the pathology and demographics of congenital and infant acute leukemia, investigate the differences, describe these differences, and evaluate the reasons for these differences.

During the disease course, patients present in different clinical environments and are diagnosed by different methodologies and treated by similar national clinical guidelines; their disease pathologies are dominated by the specific types of leukemia with unique clinical outcomes. Through the application of the principles scientific nosology, sufficient-component cause model, social ecology theory, and molecular pathological epidemiology, this investigator found factors associated with the evolution and development of disease.

The research questions in this dissertation study prompted a comprehensive investigation of the under 12 months of age population diagnosed with acute leukemia in the US from 2008 to

2014. The following chapter includes the clinical presentation of patients with congenital and infant leukemia diagnosis and identifies characteristics of the diagnostic odyssey: lineages affected, demographics, socio-economic characteristics, treatments, and outcomes. Through a combination of descriptive statistics and classification, this investigator addressed the dearth of pathology data in the literature for this population.

Data Analysis

This investigator evaluated diagnoses of acute leukemia to address the gap in the literature regarding the pathology and demographic data available for children under 12 months of age. All records of infants diagnosed with acute leukemia (A-AL) under 12 months of age from 2008 to 2014 in the SEER registry were extracted and subsequently evaluated in SPSS. To organize and understand the groups from the case series prior to analysis of collected variables, a flowchart was generated (see Figure 2). The AL group was divided into all AML diagnoses under 12 months (A-AML), all ALL diagnoses under 12 months (A-ALL), all acute leukemia of ambiguous lineage (ALAL) diagnoses under 12 months (A-ALAL) and an "other" category for uncategorized other acute leukemia (OAL, A-COAL). The final two lineage groups were generated given not all infant acute leukemia retrieved from the SEER registry are consistent with the two distinct lineages myeloid characteristic of AML or lymphoid characteristic of ALL but also mixed lineage characteristic of ALAL and an "other" category for uncategorized or undetermined lineage involved in OAL. To evaluate the differences in presentation between the two populations based on the age from birth to less than 12 months, infants were placed into congenital ([C], birth to < 2 months) and infant ([I], ≥ 2 months to < 12 months) age groups for each of the respective lineage stratified groups: C-AML, I-AML, C-ALL, I-ALL, C-ALAL, I-ALAL, C-OAL, and I-OAL.

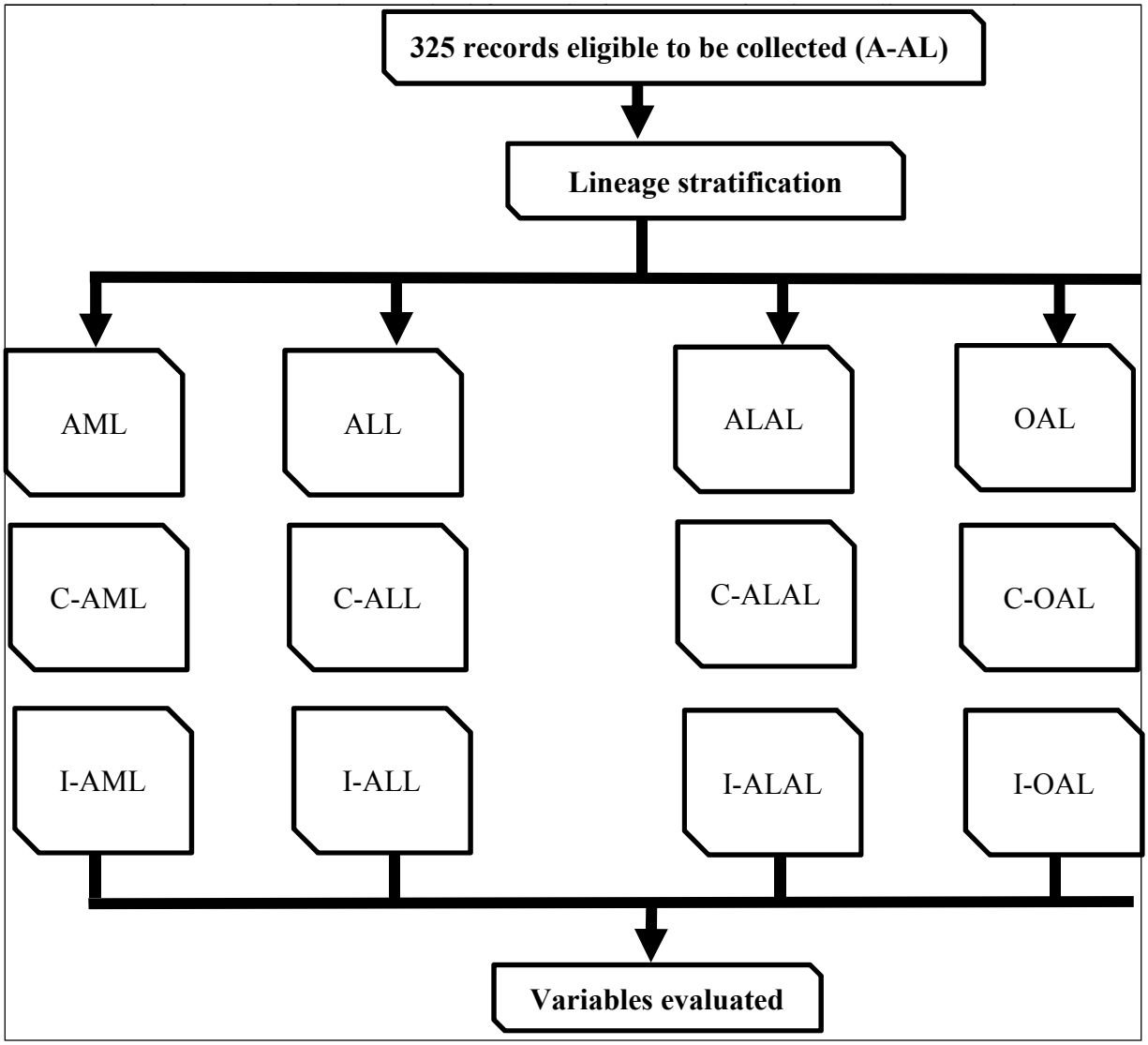


Figure 2. Flow of data analysis in dissertation study. Data analysis of acute leukemia profiles of 325 infants < 12 months of age at diagnosis from the SEER database, 2008-2014.

characteristics of the group and individual records. After extraction of the data from the SEER*Stat software, the data were entered into SPSS as a single file. SPSS facilitates the process of evaluating data via the simple descriptive process for values of characteristics and through quantitative calculations, which provides complex analysis of data groups. There were 325 records of acute leukemia diagnoses eligible to be collected from the SEER registry from 2008 to 2014. The 325 records were stratified by the lineage affected: myeloid (AML), lymphoid (ALL), ambiguous lineage acute leukemia, and other acute leukemia. The AML, ALL, ALAL,

and OAL groups were subsequently stratified by age: C-AML, I-AML, C-ALL, I-ALL, C-ALAL, I-ALAL, C-OAL, and I-OAL. Subsequent files were generated for each of these groups to evaluate the distinctive characteristics of the records within SPSS. The most recent SPSS Version 25 includes descriptive statistical modules for frequencies, descriptive, and crosstabulation. The principal investigator of this study used these functions to manipulate data to generate the following figures and tables included in this chapter. All acute leukemia lineage-age-stratified groups were evaluated within SPSS for each collected variable.

Findings

Case Series Evaluation

Prior to addressing the research questions in this dissertation study, the case series data were evaluated as a group to ensure patients were appropriately classified prior to initiating further studies. The final case series included 325 records extracted from the SEER registry that were divided into eight groups: C-AML, I-AML, C-ALL, I-ALL, C-ALAL, I-ALAL, C-OAL, and I-OAL. The largest group, I-ALL, included 141 diagnoses, followed by I-AML with 113 diagnosis, C-AML with 34 diagnoses, C-ALL with 18 diagnoses, I-ALAL with 10 diagnoses, C-OAL with five diagnoses, C-ALAL and I-OAL with two diagnoses each, respectively (see Figure 3). There were 180 males and 145 females in the case series.

Prior to addressing the research questions in this dissertation study, the case series data were evaluated as a group to ensure patients were appropriately diagnosed prior to initiating further studies. The case series was placed into acute leukemia lineage age stratified groups before addressing the research questions (see Figure 2).

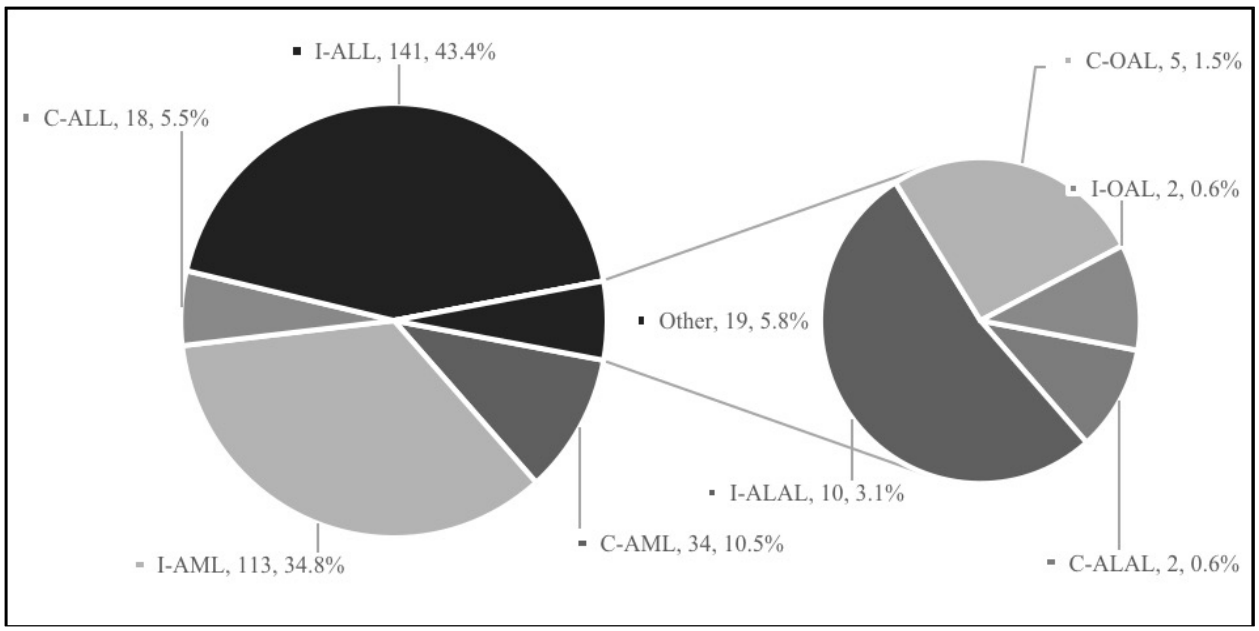


Figure 3. Acute leukemia age stratified profiles of infant case series. Acute leukemia profiles of 325 infants under 12 months of age at diagnosis from the SEER database, 2008-2014. Cases retrieved from the SEER database diagnosed from 2008-2014 by age stratified lineage groups. The age at diagnosis and the leukemia lineages involved define groups. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). C-AML = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months).

The 325 records included in the case series extracted from the SEER registry were diagnosed with a variety of confirmation methodologies in the laboratory: microscopically confirmed (310, 95.4%) and not microscopically confirmed (15, 4.6%; see Figure 4). The majority of cases were diagnosed via a microscopically confirmed methodology. The microscopically confirmed category was further divided by diagnostic confirmation modality: (a) positive histology (245, 76.6%); (b) positive exfoliative cytology, no positive histology (8, 2.5%); (c) positive histology AND immunophenotyping AND/OR positive genetic studies (57, 17.8%); and (d) positive microscope confirmation, method not specified (there were no cases diagnosed with this method). Of the cases diagnosed with a microscopically confirmed method,

positive histology methodology was used in the majority of cases; under 20% of cases were diagnosed with a methodology that may have included an informative genetic test.

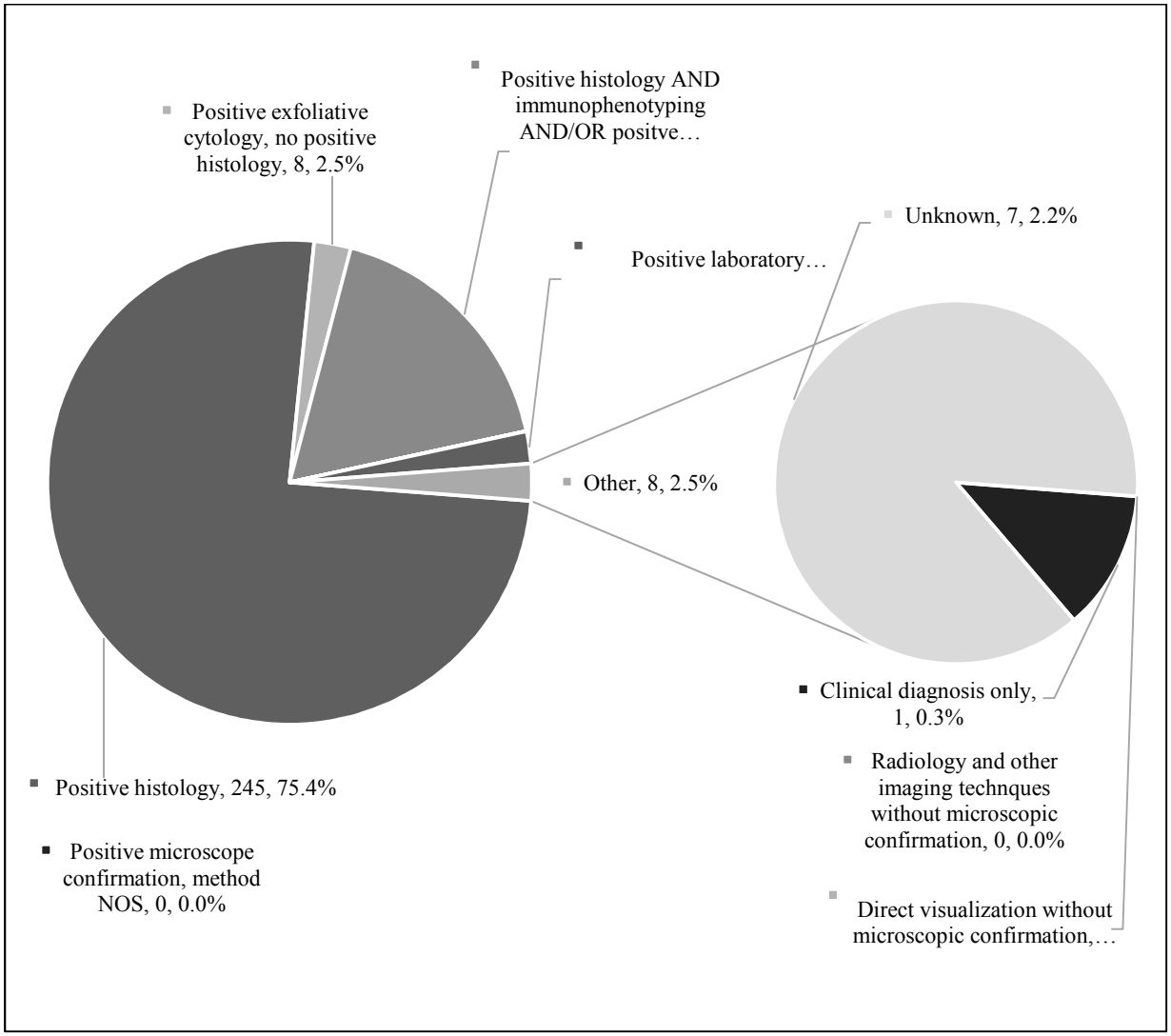


Figure 4. Diagnostic confirmation methodology of infant case series. Diagnostic confirmation methodology of acute leukemia in 325 infants < 12 months of age at diagnosis from the SEER database, 2008-2014. The case series stratified by microscopically confirmed methodologies, unknown, and non-microscopically confirmed methodologies used to diagnose acute leukemia.

The not microscopically confirmed category was further divided by diagnostic confirmation modality: (a) positive laboratory test/marker study (7, 2.2%), (b) direct visualization without microscopic confirmation (there were no cases diagnosed with this method), (c) radiology and other imaging techniques without microscopic confirmation (there were no cases diagnosed with

this method), and (d) clinical diagnosis only (1, 0.3%). Of the cases diagnosed with a non-microscopically confirmed method, positive laboratory test/marker study was used in the majority of cases; under 3% of cases were diagnosed with a methodology that may have included an informative genetic test. A single case was diagnosed with clinical indication only; all other cases included in the case series were diagnosed with a laboratory diagnostic confirmation methodology.

Research Questions

Research questions 1 and 2. "What is the distinctive clinical presentation of children diagnosed with congenital and infant AML and ALL under 1 year of age in the SEER database between 2008-2014 in the United States?" To address Research Question 1, the infants diagnosed with acute leukemia were divided into AML, ALL, ALAL, or OAL, given not all infant acute leukemia retrieved from the SEER registry were consistent with the two distinct lineages myeloid (AML), lymphoid (ALL), but also acute leukemia of ambiguous lineage and an "other" category for uncategorized other acute leukemia. These distinct groups were evaluated to address Research Question 1 followed by Research Question 2, "What is the epidemiological profile of cases of congenital and infant leukemia AML and ALL in the SEER database between 2008 to 2014 in the United States?" as described herein to address the distinctive clinical presentation and epidemiological profile of children diagnosed with congenital and infant acute leukemia under 12 months of age in the SEER database between 2008 to 2014 in the United States.

The clinical presentation and epidemiology profile included collection of data related to and an evaluation of (a) year of diagnosis (diagnosis period); (b) SEER registry data (including type of reporting clinic or hospital, registry, rural-urban location, county, state-county, and state);

(c) estimated age at diagnosis; (d) sex; (e) race; (f) disease primary site; (g) histology and behavior; (h) diagnostic confirmation methodology (methodologies for clinical diagnostics of each test strategy); (i) ICD-O-3/WHO 2008 morphology group, subtype, and classification; (j) treatment; (k) cause of death; (l) survival months to current or COD; (m) vital status; (n) insurance status; and (o) socioeconomic variables (% of persons in county under age 18 years, % families below poverty levels, % unemployed, number of foreign born, and median household income).

Distinctive presentation of congenital and infant AML less than 12 months. The infants diagnosed with AML included those from birth to less than 2 months (C-AML), and those aged 2 months or more to less than 12 months (I-AML) were evaluated in single group: all infants under 12 months of age at diagnosis with acute myeloid leukemia (A-AML). The A-AML group was evaluated for characteristics, including the number of infants diagnosed with C-AML and I-AML. The A-AML group included 147 infants, which were composed 45.2% of the 325 AL infant case series (see Table 8).

The C-AML group included 34 infants, composed of 23.1% of the A-AML group and 10.4% of the AL case series, and the I-AML group included 113 infants, composed of 76.8% of the A-AML group and 34.7% of the AL case series (see Figure 3). The estimated age at diagnosis in months calculated from months since last birthday was evaluated with a mean age of 5.8 months plus or minus *SD* 3.8 for infants diagnosed with AML. The A-AML group was evaluated for the sex of infants, and there were 78 males (53.1%) and 69 females (46.9%) diagnosed (see Figure 7). The A-AML group was evaluated for race and ethnicity of the infants: (a) Caucasian (White), (b) African-American (Black), (c) Asian or Pacific Islander, (d) American Indian or Alaska Native, and (d) unknown race; ethnicity was classified as Hispanic or non-

Hispanic. The race and ethnicity data of A-AML included (a) 110 Caucasians (White), 45 Hispanic, and 65 Non-Hispanic infants; (b) 22 African-American (Black), two Hispanic and 20 Non-Hispanic infants; (c) 11 Asian or Pacific Islander, one Hispanic, and 10 Non-Hispanic infants; (d) one American Indian or Alaska Native Non-Hispanic infant; and (e) three unknown race Non-Hispanic infants (see Table 8 and Figure 8).

Table 8
Demographic profiles of 147 infants with Acute Myeloid Leukemia from the SEER Database, 2008-2014 for Leukemia Lineage Age Groups

Variables	*N* (A-AL %, 325)	C-AML, *N* (%A-AML; % AL)	I-AML, *N* (%A-AML; %AL)
	147 (45.2%)	34 (23.1%; 10.4%)	113 (76.8%; 34.7%)
Age			
Estimated age at diagnosis (months)	Mean ± *SD*	Median	
	5.8 ± 3.8	6.0	
Sex			
N (% A-AML)			
Male	78 (53.1%)	17 (50%)	61 (54.0%)
Female	69 (46.9%)	17 (50%)	52 (46.0%)
Race *N* (%)	Non-Hispanic (% race)	Hispanic (% race)	Total (race % of AML, *N* = 147)
Caucasian (White)	65 (59.0%)	45 (40.9%)	110 (74.8%)
C-AML	8	14	22
I-AML	57	31	88
African-American (Black)	20 (90.9%)	2 (9.1%)	22 (14.9%)
C-AML	4	**	4
I-AML	16	2	18
Asian or Pacific Islander	10 (90.9%)	1 (9.1%)	11 (7.5%)
C-AML	6	**	6
I-AML	4	1	5
American Indian or Alaska Native	1 (100.0%)	**	1 (0.68%)
C-AML	**	**	**
I-AML	1	**	1
Unknown	3 (100.0%)	**	3 (2.04%)
C-AML	2	**	2
I-AML	1	**	1

Note. AL = acute leukemia. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). **Null cases reported in this subtype.

The AML diagnoses were age stratified by leukemia type C-AML or I-AML (see Figure 5). The C-AML group included 34 infants composed of 23.1% of the A-AML group and 10.4% of the AL case series. The I-AML group included 113 infants composed of 76.8% of the A-AML group and 34.7% of the AL case series (see Figure 3).

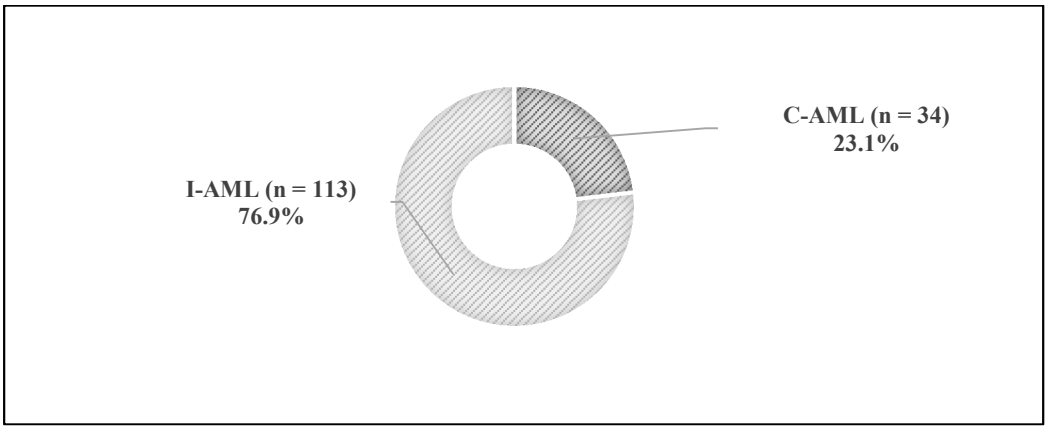


Figure 5. Age stratified leukemia type of AML infants less than 12 months. Age stratified leukemia groups of the cases retrieved from the SEER database from 2008-2014 diagnosed with acute myeloid leukemia. All infants from birth to < 2 months are placed into a congenital disease age group, and those age ≥ 2 months to < 12 months are placed into an infant age group. Subsequently, infants are placed into age-stratified leukemia groups. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months).

The estimated age at diagnosis distribution of the A-AML group was calculated from months since last birthday entered into the SEER registry. The majority of AML diagnoses (24) occurred in the C-AML in the infants from birth to less than 1 month of age. In addition, the other peak age of diagnoses (21) with AL within the case series occurred in patients from 11 months or more to less than 12 months of age. Additional diagnoses include 10 infants from one month or more to less than 2 months, four aged 2 months or more to less than 3 months, 4 aged 3 months or more to less than 4 months, 12 aged 4 months or more to less than 5 months, 11 aged 5 months or more to less than 6 months, 10 aged 6 months or more to less than 7 months, 12 aged 7 months or more to less than 8 months, 15 aged 8 months or more to less than 9 months,

14 aged 9 months or more to less than 10 months, and 10 aged 10 months or more to less than 11 months of age (see Figure 6). The mean age of infant diagnoses under 12 months of age with AML was 5.8 months, or 5 months and approximately 24 days of age with a SD of 3.8 months.

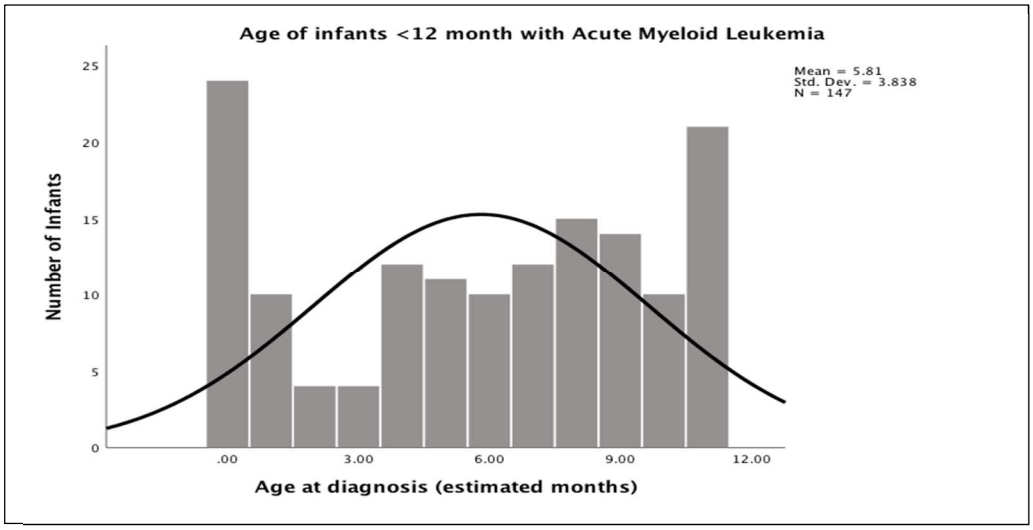


Figure 6. Acute myeloid leukemia age distribution. Age at diagnosis with acute myeloid leukemia for 147 infants (< 12 months of age) from the SEER database, 2008-2014. Estimated age at diagnosis in months is calculated from months since last birthday derived from month of diagnosis subtracted from birth month as entered into SEER.

The A-AML diagnoses (147) were stratified by sex: male or female; there were no diagnoses entered without a sex assigned to the SEER record (see Figure 7). The group was then assessed for the distribution of sex within the A-AML group. There were 78 males composed 47% of the AML diagnoses. There were 69 females composed 53% of the AML diagnoses.

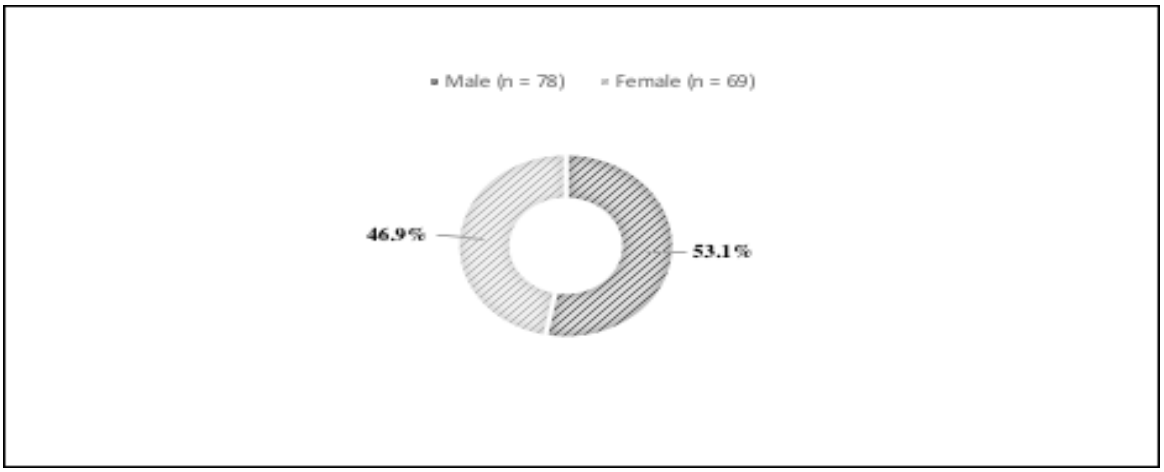
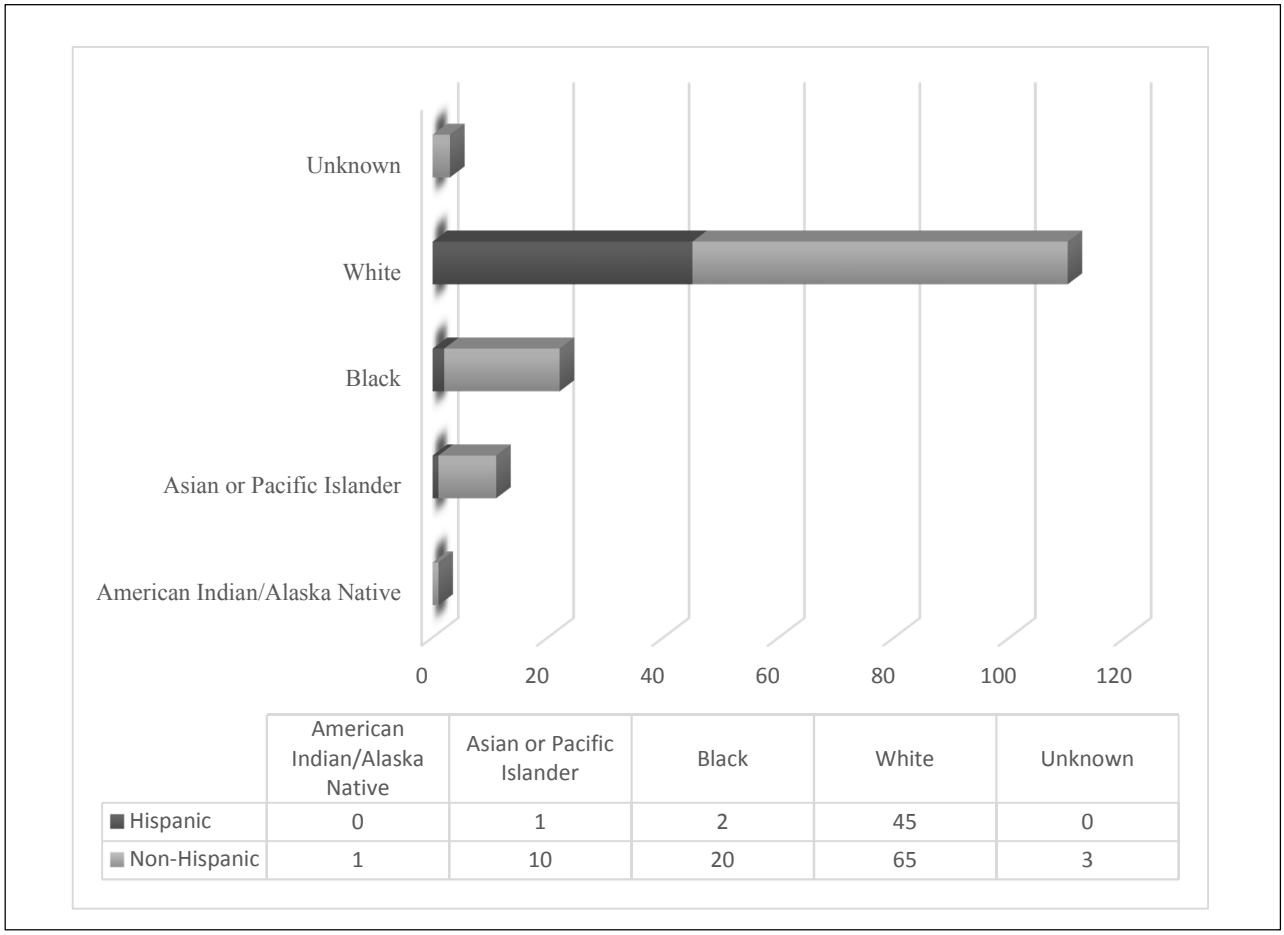


Figure 7. Sex of infants less than 12 months with acute myeloid leukemia**.** Sex distribution for 147 infants (< 12 months of age) diagnosed with acute myeloid leukemia from the SEER database, 2008-2014.

The A-AML diagnoses (147) were stratified by race and ethnicity of the infants: (a) Caucasian (White), (b) African American (Black), (c) Asian or Pacific Islander, (d) American Indian or Alaska Native, and (e) unknown race; ethnicity included Hispanic or non-Hispanic infants (see Figure 8). The highest number of diagnoses occurred in non-Hispanic Caucasians (White, 65), and the second largest number of diagnoses in Hispanic Caucasians (White, 45) infants. Diagnoses in African-American (Black) non-Hispanic infants (20) were the majority within the race; there were only two African American Hispanic infants diagnosed. Diagnoses in the combined Asian or Pacific Islander group were dominated by non-Hispanic infants (10); there was only a single Hispanic infant diagnosed. The least number of diagnoses occurred in the combined American Indian or Alaskan Native group in a single non-Hispanic infant. Three records had no known race but were designated as non-Hispanic ethnicity.

Diagnoses placed into the A-AML group were first divided by C-AML and I-AML, then evaluated by the designated ICD-O-3/WHO 2017 aligned leukemia group acute myeloid



	American Indian/Alaska Native	Asian or Pacific Islander	Black	White	Unknown
Hispanic	0	1	2	45	0
Non-Hispanic	1	10	20	65	3

Figure 8. Race and ethnicity of infants with acute myeloid leukemia less than 12 months. Race and ethnicity of 147 infants (< 12 months of age) diagnosed with acute myeloid leukemia from the SEER database, 2008-2014.

leukemia and related neoplasms and further defined by subgroups and subtypes. All infant diagnoses from the acute myeloid leukemia and related neoplasms group were divided into acute myeloid leukemia with balanced translocations/inversions (subgroup), AML with myelodysplasia-related changes (subgroup, subtype), therapy-related myeloid neoplasms (subgroup, subtype), and AML not otherwise specified (subgroup, see Table 9 and Figure 9).

Table 9
WHO 2017 Classification of Myeloid Malignancies Groups, Subgroups, and Subtypes of 147 Infants with Acute Myeloid Leukemia by Age Stratified Groups from the Surveillance, Epidemiology, and End Results (SEER) Database, 2008-2014

	N (% A-AL, 325)	*N* (%A-AML, 147)	*N* (% of C-AML, 34)	*N* (% of I-AML, 113)
Acute myeloid leukemia with balanced translocations/inversions (Subgroup)	15 (4.6%)	15 (10.2%)	5 (44.1%)	10 (8.84 %)
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	**	**	**	**
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	1 (0.30%)	1 (0.68%)	**	1 (0.88%)
APL with *PML-RARA*	2 (0.62%)	2 (1.36%)	1 (2.9%)	1 (0.88%)
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL) *variant KMT2A translocations in acute leukemia*	11 (3.4%)	11 (7.5%)	3 (8.8%)	8 (7.07%)
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	**	**	**	**
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*	**	**	**	**
AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*	1 (0.30%)	1 (0.68%)	1 (2.9%)	**
AML with *BCR-ABL1*	**	**	**	**
Acute myeloid leukemia with gene mutations			**	
AML with mutated *NPM1*	**	**	**	**
AML with biallelic mutations of *CEBPA*	**	**	**	**
AML with mutated *RUNX1*	**	**	**	**
AML with myelodysplasia-related changes (Subgroup, Subtype)	1 (0.30%)	1 (0.68%)	**	1 (0.88%)
Therapy-related myeloid neoplasms (Subgroup, subtype)	**			

(continued)

	N (% A-AL, 325)	*N* (%A-AML, 147)	*N* (% of C-AML, 34)	*N* (% of I-AML, 113)
AML NOS (Subgroup)	131 (40.3%)	131 (89.1%)	29 (22.4%)	101 (89.3%)
AML NOS	61 (18.8%)	61 (41.5%)	15 (44.1%)	46 (40.7%)
AML with minimal differentiation	4 (1.2%)	4 (2.72%)	1 (2.9%)	3 (2.7%)
AML without maturation	1 (0.30%)	1 (0.68%)	**	1 (0.90%)
AML with maturation	3 (0.92%)	3 (2.04%)	1 (2.9%)	2 (1.8%)
Acute myelomonocytic leukemia	6 (1.8%)	6 (4.08%)	**	6 (5.4%)
Acute monoblastic and monocytic leukemia	28 (8.6%)	28 (19.0%)	4 (11.8%)	24 (21.6%)
Pure erythroid leukemia	**	**	**	**
Acute megakaryoblastic leukemia	26 (7.7%)	26 (17.7%)	7 (20.6%)	19 (12.9%)
Acute basophilic leukemia	**	**	**	**
Acute panmyelosis with myelofibrosis	1 (0.30%)	1 (0.68%)	1 (2.9%)	**
Myeloid leukemia NOS≠	1 (0.30%)	1 (0.68%)	**	1 (0.90%)

Note. Acute myeloid leukemia and related neoplasms, % of A-AL = 45.2%. A-AML = all cases < 12 months of acute myeloid leukemia. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). AL = acute leukemia; **Null cases reported in this subtype. ≠Not a WHO 2017 defined subtype. Not otherwise specified = NOS.

These subgroups were further subdivided by the ICD-O-3/WHO 2017 aligned subtypes. Acute myeloid leukemia with balanced translocations/inversions subgroup included 15 diagnoses (4.6% of AL) with genetic data supporting the diagnosis of "AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11"*; "AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*" in a single infant, respectively; and "APL with *PML-RARA*' in two infants. The "AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* (MLL) *& variant KMT2A translocations in acute leukemia*" subtype was the largest with 11 diagnoses (3.4% of AL). The AML with myelodysplasia-related changes subgroup, and subtype included a single infant diagnostic case.

The AML not otherwise specified subgroup, meaning leukemia without features to be placed into other categories by comprehensive morphology, immunophenotyped and genetics

data included the majority of A-AML diagnoses (131, 40.3 % of AL). Within the AML not otherwise specified subgroup, the AML not otherwise specified subtype diagnoses (61, 18.8% of AL) dominated, followed by acute monoblastic and monocytic leukemia subtype diagnoses (28, 8.6% of AL), and acute megakaryoblastic leukemia subtype (26, 7.7% of AL). In addition, the

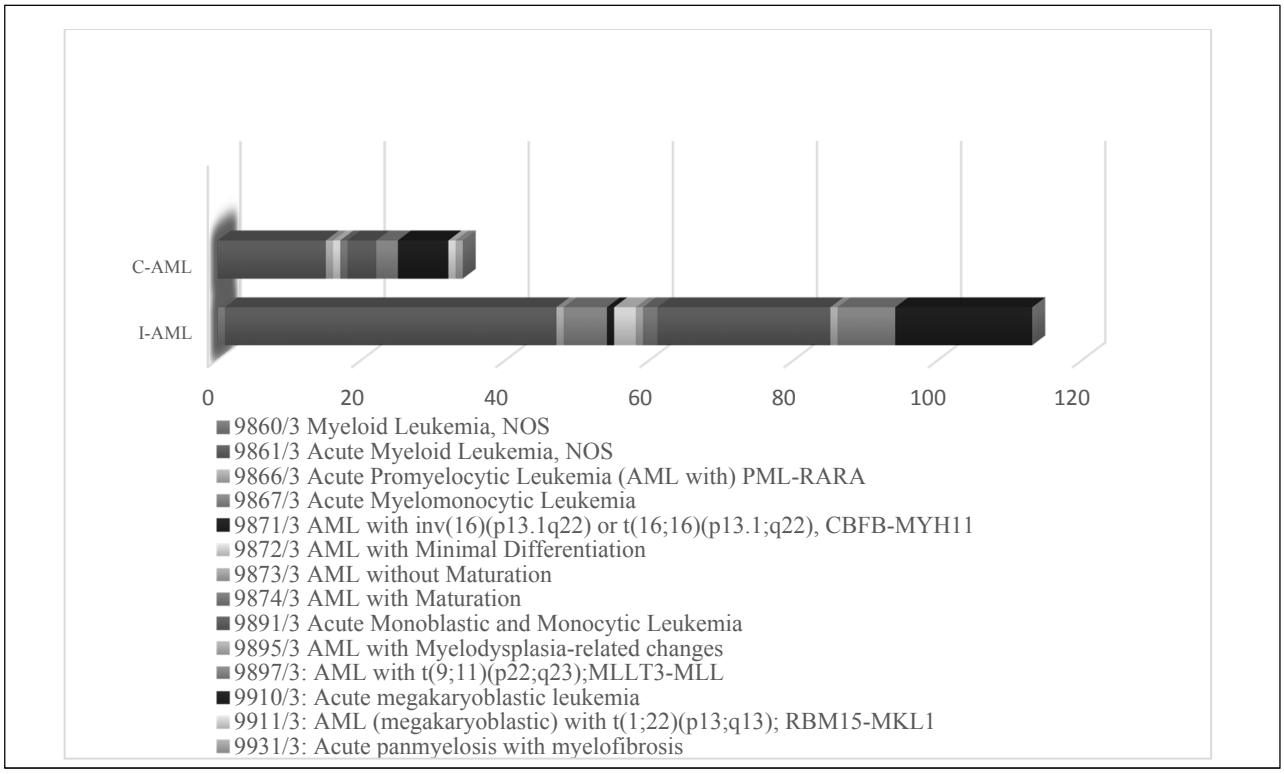


Figure 9. WHO AML 2017 subtypes in infants under 12 months of age at diagnosis. WHO AML 2017 subtypes of 147 infants < 12 months of age at diagnosis from the SEER database, 2008-2014.

remaining diagnoses in the subgroup included six in the acute myelomonocytic leukemia; four in the AML with minimal differentiation; three in the AML with maturation; and a single case in the following subtypes of AML without maturation, acute panmyelosis with myelofibrosis, and myeloid leukemia, NOS.

Epidemiological data. Diagnoses placed into the A-AML group were first divided by C-AML and I-AML, then evaluated by the registry reporting source. The registry reporting sources

for A-AML included hospital inpatient/outpatient or clinic (144) and laboratory only (hospital or private [3], see Table 10). The C-AML group was reported by hospital inpatient/outpatient or clinic (33) and laboratory only (hospital or private [1]), and the I-AML group was reported by hospital inpatient/outpatient or clinic (111) and laboratory only (hospital or private [2]). The majority of clinical diagnoses of AML occurred in a hospital inpatient/outpatient or clinic environment.

Table 10
Registry Reporting Source of 147 Infants with Acute Myeloid Leukemia from the SEER Database, 2008-2014

	N (% of A-AL, 325)	*N* (% of A-AML, 147)	*N* (% of C-AML, 34)	*N* (% of I-AML, 113)
Hospital inpatient/outpatient or clinic	144 (44.3%)	144 (97.9%)	33 (97.0%)	111 (98.2%)
Laboratory only (hospital or private)	3 (0.92%)	3 (2.04%)	1 (2.94%)	2 (1.76 %)

Note. A-AML group, % of AL = 45.2%. AL = acute leukemia. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months).

Diagnoses placed into the A-AML group were first divided by C-AML and I-AML, then evaluated by the disease primary site. The disease primary site as anticipated for all patients was the bone marrow (see Table 11). As leukemias are clonal hematopoietic stem cells disorders generally defined by the presence of 20% or more bone marrow involvement, the primary site of disease serves as an internal control that the appropriate diagnoses had been assigned and the patient should be included in the case series.

Table 11
Disease Primary Site of 147 Infants with Acute Myeloid Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (% of A-AML, 147)	*N* (% of C-AML, 34)	*N* (% of I-AML, 113)
C42.1-bone marrow	147 (100%)	147 (100%)	147 (100%)	147 (100%)

Note. A-AML group, % of A-AL= 45.2%. C42.1 = ICD-O-3 code. AL = acute leukemia. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months).

Diagnoses placed into the A-AML group were first divided by C-AML and I-AML, then evaluated by the diagnostic confirmation methodology. The methodologies used for A-AML included clinical diagnosis only (1); positive histology and immunophenotyping AND/OR positive genetic studies (23); positive exfoliative cytology, no positive histology (5); positive histology (115); positive laboratory test/marker study (2); and unknown source (1), see Table 12). The C-AML group was confirmed by clinical diagnosis only (1); positive histology and immunophenotyping AND/OR positive genetic studies (5); positive exfoliative cytology, no positive histology (2); positive histology (24); and positive laboratory test/marker study (2). The I-AML group was confirmed by positive histology and immunophenotyping AND/OR positive genetic studies (18); positive exfoliative cytology, no positive histology (3); positive histology (109); and unknown source (1). The majority of clinical diagnoses of AML were confirmed with only histology information, followed by cases, which used both positive histology and immunophenotyping AND/OR positive genetic studies to ensure the correct diagnoses.

Table 12
Diagnostic Confirmation Methodology of 147 Infants with Acute Myeloid Leukemia from the SEER Database, 2008-2014

	N (% A-AL, 325)	*N* (% AML, 147)	*N* (% of C-AML, 34)	*N* (% of I-AML, 113)
Clinical diagnosis only	1 (0.30%)	1 (0.68%)	1 (2.94%)	**
Positive histology AND immunophenotyping AND/OR positive genetic studies	23 (7.07%)	23 (15.6%)	5 (14.7%)	18 (15.9%)
Positive exfoliative cytology, no positive histology	5 (1.54%)	5 (3.4%)	2 (5.88%)	3 (2.65%)
Positive histology	115 (35.4%)	115 (78.2%)	24 (70.5%)	109 (96.4%)
Positive laboratory test/marker study	2 (0.61%)	2 (1.36%)	2 (5.88%)	**
Unknown	1 (0.30%)	1 (0.68%)	**	1 (0.88%)

Note. A-AML group, % of A-AL = 45.2%. AL = acute leukemia; C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). **Null cases reported.

Diagnoses placed into the A-AML group were first divided by C-AML and I-AML, then evaluated by insurance status (see Table 13). The insurance status included any Medicaid (60), insurance status unknown (5), insured (68), insured/no specifics (12), and uninsured ([2], see Table 6). The C-AML group insurance status distribution included (a) any Medicaid (9), (b) insurance status unknown (3), (c) insured (19), and (d) insured/no specifics (3). The I-AML group included (a) any Medicaid (51), (b) insurance status unknown (2), (c) insured (49), (d) insured/no specifics (9), and (e) uninsured (2). The majority of patients diagnosed with AML patients were insured either via private insurance or Medicaid.

Table 13
Insurance Status of 147 Infants with Acute Myeloid Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%AML, 147)	*N* (% of C-AML, 34)	*N* (% of I-AML, 113)
Any Medicaid	60 (18.4%)	60 (40.8%)	9 (26.4%)	51 (45.1 %)
Insurance status unknown	5 (1.53%)	5 (3.4%)	3 (8.82%)	2 (1.76%)
Insured	68 (20.9%)	68 (46.2%)	19 (55.8%)	49 (43.3%)
Insured/no specifics	12 (3.69%)	12 (8.16%)	3 (8.82%)	9 (7.96%)
Uninsured	2 (0.61%)	2 (1.36%)	**	2 (1.76%)

Note. A-AML group, % of A-AL =45.2%. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). AL = acute leukemia. **Null cases reported.

Distinctive presentation of congenital and infant ALL less than 12 months. The infants diagnosed with acute lymphoid leukemia included those from birth to less than 2 months (C-ALL), and those aged 2 months or more to less than 12 months (I-ALL) were evaluated in a single group: All less than 12 months at diagnosis with acute lymphoid leukemia (see Table 7). The A-ALL group was evaluated for characteristics, including number of infants diagnosed from birth to less than 2 months (C-ALL), which included 18 diagnoses, and 2 months or more to less than 12 months (I-ALL), which included 141 infants. The A-ALL group included 159 infants, which were composed 48.9% of the 325 AL infant case series (see Figure 3).

The C-ALL group included 18 infants composed of 11.3% of the A-ALL group, 5.54% of the AL case series, and the I-ALL group included 141 infants composed 88.7% of the A-ALL group and 43.3% of the AL case series (see Figure 2, Table 14). The estimated age at diagnosis in months calculated from months since last birthday was evaluated with a mean age of 6.1 months plus or minus *SD* 3.4 for infants diagnosed with ALL. The A-ALL group was evaluated

for the sex of infants. There were 92 males (57.9%) and 67 females (42.1%) diagnosed. The A-ALL group was evaluated for race of the infants: (a) Caucasian (White), (b) African-American (Black), (c) Asian or Pacific Islander, (d) American Indian or Alaska Native, and (e) unknown race. The A-ALL group was evaluated for ethnicity of the infants: Hispanic or non-Hispanic. The race and ethnicity data included (a) 116 Caucasian (White), 60 Hispanic, and 56 non-Hispanic infants; (b) 17 African-American (Black); (c) three Hispanic and 14 non-Hispanic infants; (d) 20 Asian or Pacific Islander, two Hispanic, and 18 non-Hispanic infants; (e) three American Indian or Alaska Native non-Hispanic infants; (f) three unknown race, one Hispanic, and 2 non-Hispanic infants (see Figure 13).

Table 14
Demographic Profiles of 159 Infants with Acute Lymphoid Leukemia from the SEER Database, 2008-2014 with Leukemia Lineage Age Groups

Variables	*N* (A-AL %, 325)	C-ALL, *N* (%ALL; %AL)	I-ALL, *N* (%ALL; %AL)
N	159 (48.9%)	18 (11.3%; 5.54%)	141 (88.7%; 43.3%)
Age	(Mean ± *SD*)	Median	
Estimated age at diagnosis (months)	6.18 ± 3.4	7.0	
Sex *N* (%)			
Male	92 (57.9%)	6 (33.3%)	86 (60.9%)
Female	67 (42.1%)	12 (66.7%)	55 (39.0%)
Race *N* (%)			
	Non-Hispanic (% race)	Hispanic (% race)	Total (race % of A-ALL)
Caucasian (White)	56 (48.2%)	60 (51.7%)	116 (72.9%)
	Non-Hispanic (% race)	Hispanic (% race)	Total (race % of A-ALL)
C-ALL	8	8	16

(continued)

Variables	*N* (A-AL %, 325)	C-ALL, *N* (%ALL; %AL)	I-ALL, *N* (%ALL; %AL)
I-ALL	48	52	100
African American (Black)	14 (82.3%)	3 (17.6%)	17 (10.7%)
C-ALL	**	**	**
I-ALL	14	3	17
Asian or Pacific Islander	18 (90.0%)	2 (10.0%)	20 (12.5%)
C-ALL	1	1	2
I-ALL	17	1	18
American Indian or Alaska Native	3 (100%)	**	3 (1.89%)
C-ALL	**	**	**
I-ALL	3	**	**
Unknown	3 (100%)	0	3 (1.89%)
C-ALL	**	**	**
I-ALL	2	1	3

Note. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). AL = acute leukemia. **Null cases reported.

The ALL diagnoses were age stratified by leukemia type: C-ALL or I-ALL. The C-ALL group included 18 infants composed of 11.3% of the A-ALL group and 5.54% of the AL case series. The I-ALL group included 141 infants composed of 88.7% of the A-ALL group and 43.3% of the AL case series (see Figure 10).

The estimated age at diagnosis distribution of the A-ALL group was calculated from months since last birthday entered into the SEER registry. The majority of ALL diagnoses (20) occurred in the I-ALL in the infants aged 7 months or more to less than 8 months (see Figure 11). In addition, the other peak age of diagnoses (18) with ALL within the case series occurred in patients 11 months or greater to less than 12 months. Additional diagnoses included eight infants from birth to less than 1 month, 10 aged 1 month or more to less than 2 months,

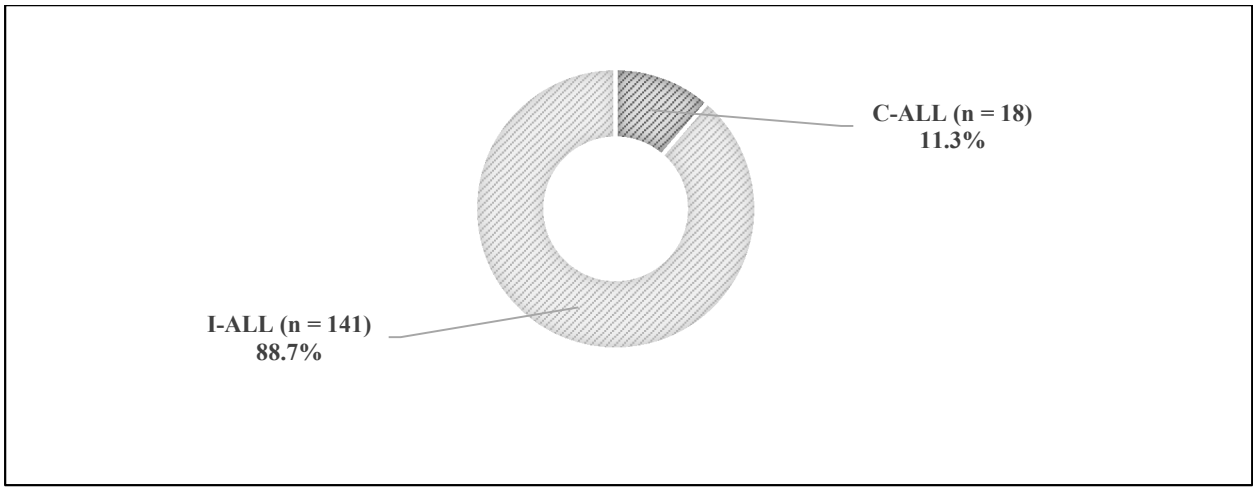


Figure 10. Age stratified leukemia type of all infants under 12 months. Age stratified leukemia groups of the cases retrieved from the SEER database from 2008-2014 diagnosed with acute lymphoid leukemia. All infants from birth to < 2 months are placed into a congenital disease age group, and those age ≥ 2 months to < 12 months are placed into an infant age group. Subsequently, infants are placed into age-stratified leukemia groups. C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months).

13 aged 2 months or more to less than 3 months, 11 aged 3 months or more to less than 4 months, 10 aged 4 months or more to less than 5 months, 12 aged 5 months or more to less than 6 months, 14 aged 6 months or more to under 7 months, 12 aged 8 months or more to less than 9 months, 14 aged 9 months or more to less than 10 months, and 17 aged 10 months or more to under 11 months of age.

The A-ALL diagnoses (159) were stratified by sex: male or female; there were no diagnoses entered without a sex assigned to the SEER record (see Figure 12). The group was then assessed for the distribution of sex within the A-ALL group. There were 92 males composed of 58.8% of the AML diagnoses. There were 67 females composed of 42.1% of the ALL diagnoses.

The A-ALL diagnoses (159) were stratified by race and ethnicity of the infants: (a) Caucasian (White), (b) African-American (Black), (c) Asian or Pacific Islander, (d) American

Indian or Alaska Native, and (e) unknown race. Ethnicity included Hispanic or non-Hispanic (see Figure 13).

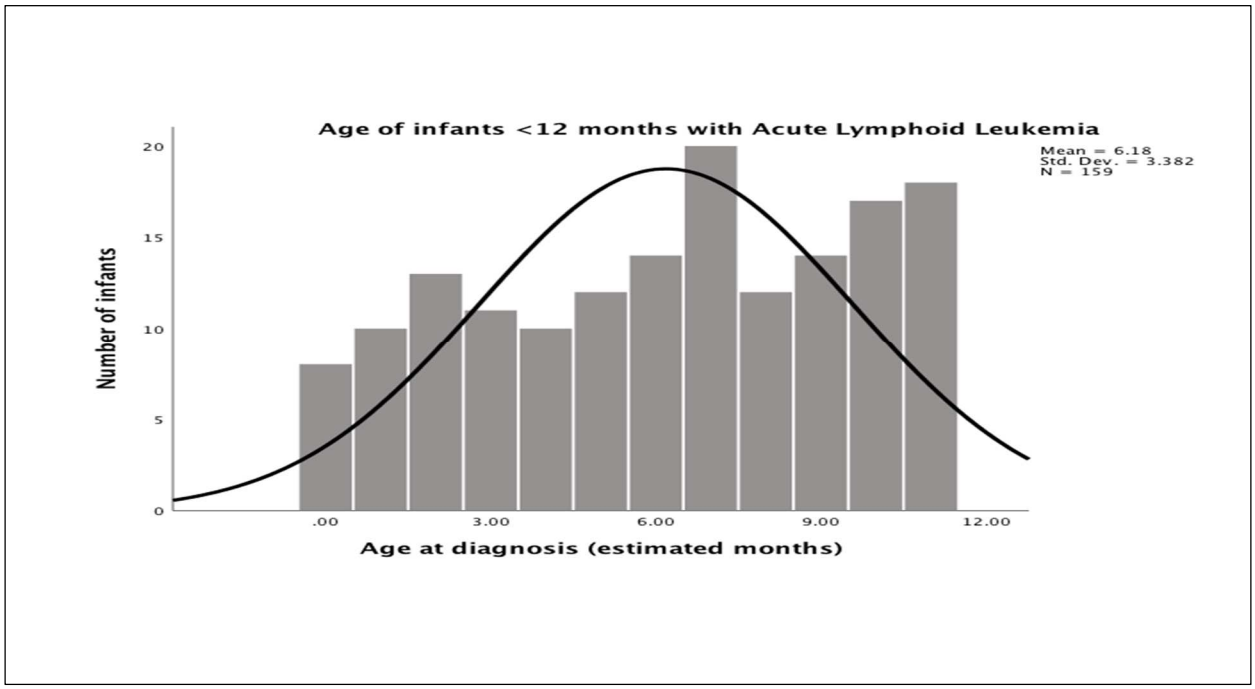


Figure 11. Acute lymphoid leukemia age distribution. Age at diagnosis with acute lymphoid leukemia for 159 infants (< 12 months of age) from the SEER database, 2008-2014. Estimated age at diagnosis in months is calculated from months since last birthday.

The highest number of diagnoses occurred in Hispanic Caucasian (White [60]), and the second largest number of diagnoses occurred in non-Hispanic Caucasian (White) infants (56). Diagnoses in the combined Asian or Pacific Islander followed with the majority as non-Hispanic infants (18); there were only two Hispanic infants diagnosed. Diagnoses in African-American (Black) non-Hispanic infants (14) were the majority within the race; there were three African American Hispanic infants diagnosed. The least number of diagnoses occurred in the combined American Indian or Alaskan Native group in three non-Hispanic infants. Three records had no known race but were designated as non-Hispanic (2) and Hispanic (1) ethnicity.

Diagnoses placed into the A-ALL group were first divided by C-ALL and I-ALL, then evaluated by the designated ICD-O-3/WHO 2017 aligned leukemia group acute lymphoid leukemia and related neoplasms and further defined by subgroups and subtypes (see Table 15). All infant diagnoses from the acute lymphoid leukemia and related neoplasms group

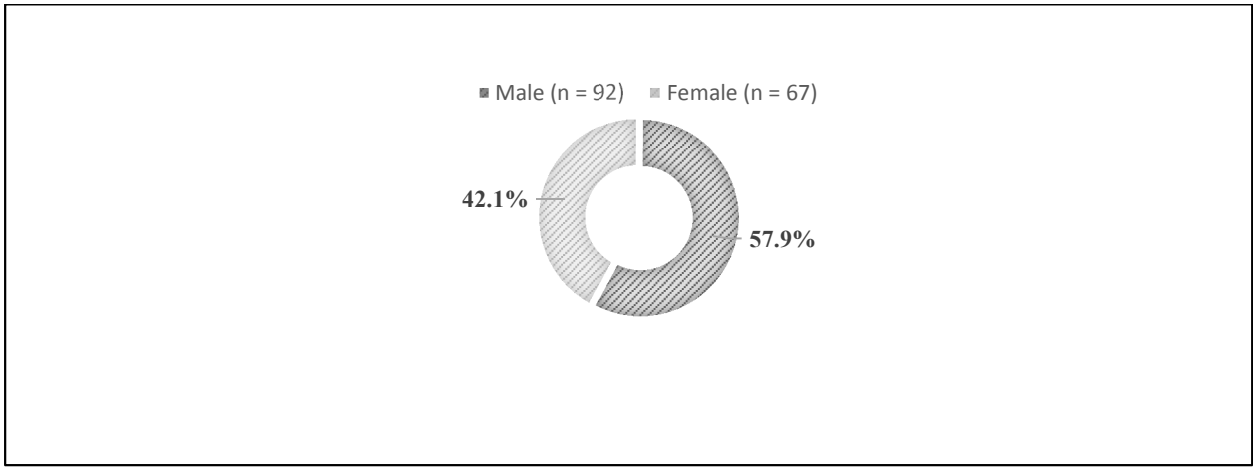
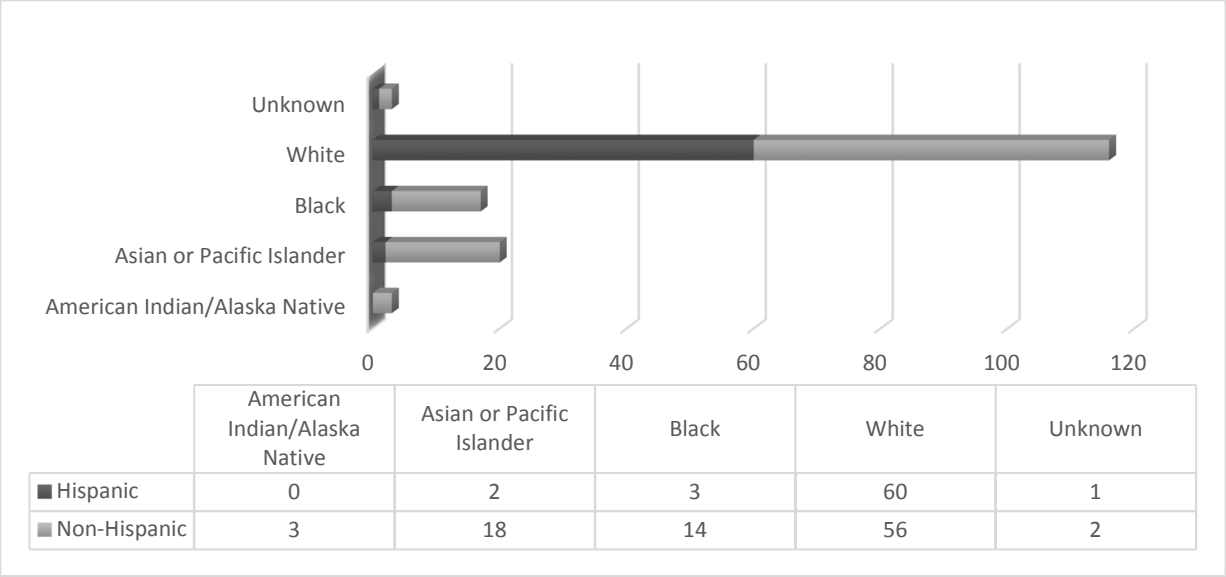


Figure 12. Sex of infants less than12 months with acute lymphoid leukemia. Sex distribution for 159 infants (< 12 months of age) diagnosed with acute lymphoid leukemia from the SEER database, 2008-2014.

were divided into B-lymphoblastic and leukemia/lymphoma, NOS (subgroup, subtype); B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities (subgroup); T-lymphoblastic leukemia/lymphoma (subgroup), and NK cell lymphoblastic leukemia/lymphoma (subgroup, subtype).



	American Indian/Alaska Native	Asian or Pacific Islander	Black	White	Unknown
Hispanic	0	2	3	60	1
Non-Hispanic	3	18	14	56	2

Figure 13. Race and ethnicity of infants with acute lymphoid leukemia less than12 months. Race and ethnicity for 159 infants (< 12 months of age) diagnosed with acute lymphoid leukemia from the SEER database, 2008-2014.

These subgroups were further subdivided by the ICD-O-3/WHO 2017 aligned subtypes (see Figure 14). B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities (subgroup) had 24 diagnoses (7.38% of AL) with genetic data supporting the diagnosis of B-lymphoblastic and leukemia/lymphoma with hyperdiploidy and "B-lymphoblastic and leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1"* in a single infant, respectively,

Table 15
2017 WHO Classification of Precursor Lymphoid Malignancies Groups, Subgroups, and Subtypes of 159 infants with Acute Lymphoid Leukemia by Age Stratified Groups from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%A-ALL, 159)	*N* (% of C-ALL, 18)	*N* (% of I-ALL, 141)
B-lymphoblastic and leukemia/lymphoma, NOS (Subgroup, Subtype)	(123, 37.8%)	(123, 77.3%)	(17, 94.4%)	(106, 75.7%)
B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities (Subgroup)	(24, 7.38%)	(24, 15.0%)	(1, 5.55%)	(23, 16.3%)
B-lymphoblastic and leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1*	**	**	**	**
B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A rearranged*	16 (4.92%)	16 (10.0%)	(1, 5.55%)	(15, 10.7%)
B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*	**	**	**	**
B-lymphoblastic and leukemia/lymphoma with hyperdiploidy	1 (0.30%)	1 (0.63%)	**	1 (0.71%)
B-lymphoblastic and leukemia/lymphoma with hypodiploidy	6 (1.84%)	6 (3.77%)	**	6 (4.25%)
B-lymphoblastic and leukemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3*	**	**	**	**
B-lymphoblastic and leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*	1 (0.30%)	1 (0.63%)	**	1 (0.71%)
B-lymphoblastic and leukemia/lymphoma, *BCR-ABL1-like*	**	**	**	**
B-lymphoblastic and leukemia/lymphoma with iAMP21	**	**	**	**
T-lymphoblastic leukemia/lymphoma (Subgroup)	12 (3.69%)	12 (7.54%)	**	12 (8.57%)
Early T-cell precursor lymphoblastic leukemia	**	**	**	**
NK cell lymphoblastic leukemia/lymphoma (Subgroup, subtype)	**	**	**	**

Note. N = 159. Acute lymphoid leukemia and related neoplasms group, % of A-AL = 49.4%. A-ALL = all cases < 12 months of acute lymphoid leukemia. C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). AL = acute leukemia. **Null cases reported in this subtype.

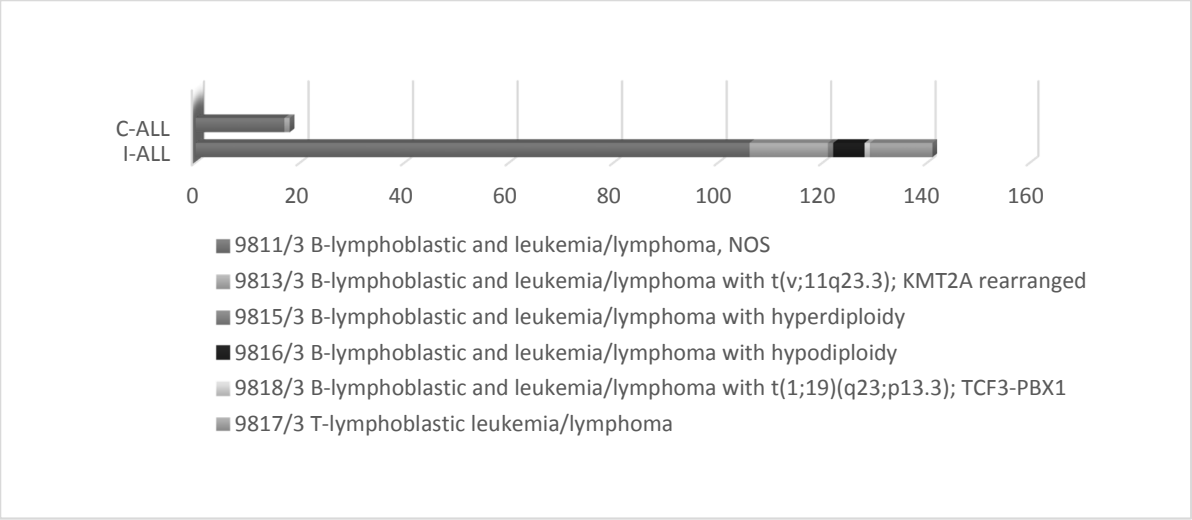


Figure 14. WHO ALL 2017 subtypes of 159 infants under 12 months of age at diagnosis from the SEER database, 2008-2014.

B-lymphoblastic and leukemia/lymphoma with hypodiploidy in six infants and the "B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A rearranged*" subtype were the largest with 16 diagnoses (4.9% of AL), and T-lymphoblastic leukemia/lymphoma (subgroup) included 12 cases. The B-lymphoblastic and leukemia/lymphoma, NOS subgroup, which is leukemia without features, was placed into other categories by comprehensive morphology. Immunophenotyped and genetics data included the majority of A-ALL diagnoses (123, 37.4 % of AL). The B-lymphoblastic and leukemia/lymphoma, NOS subgroup is also a subtype and is not further divided by ICD-O-3/WHO 2017.

Epidemiological data. Diagnoses placed into the A-ALL group were first divided by C-ALL and I-ALL, then evaluated by the registry reporting source. The registry reporting sources for A-ALL included hospital inpatient/outpatient or clinic (156, 48%), laboratory only (hospital or private; 1, 0.30%), death certificate only (1, 0.30%), and other hospital outpatient unit or surgery center (1, 0.30%; see Table 16). The C-ALL group was reported by hospital inpatient/outpatient or clinic (17, 94.4%) and equally by laboratory only (hospital or private),

death certificate only, and other hospital outpatient unit or surgery center (1, 5.56%) similar to the I-ALL group reported by hospital inpatient/outpatient or clinic (139, 98.5%) and equally by laboratory only (hospital or private), death certificate only (1, 0.71%), and other hospital outpatient unit or surgery center (1, 0.71%). The majority of clinical diagnoses of ALL occur in a hospital inpatient/outpatient or clinic environment.

Table 16
Registry Reporting Source of 159 Infants with Acute Lymphoid Leukemia from the SEER Database, 2008-2014

	N (%AL, 325)	*N* (% ALL, 159)	*N* (% C-ALL, 18)	*N* (% I-ALL, 141)
Hospital inpatient/outpatient or clinic	156 (48.0%)	156 (98.1%)	17 (94.4%)	139 (98.5%)
Laboratory only (hospital or private)	1 (0.30%)	1 (0.63%)	**	1 (0.71%)
Death certificate only	1 (0.30%)	1 (0.63%)	**	1 (0.71%)
Other hospital outpatient unit or surgery center	1 (0.30%)	1 (0.63%)	1 (5.56%)	**

Note. A-ALL group, % of A-AL = 49.4%. A-ALL = all cases <12 months of acute lymphoid leukemia. C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). AL = acute leukemia. **Null cases reported.

Diagnoses placed into the A-ALL group were first divided by C-ALL and I-ALL, then evaluated by the disease primary site. The disease primary site as anticipated for all patients was the bone marrow (see Table 17). The disease primary site as anticipated for all patients was the bone marrow: C42.1. As leukemia are clonal hematopoietic stem cells disorders generally defined by the presence of 20% or more bone marrow involvement, the primary site of disease serves as an internal control that the appropriate diagnoses have been assigned and the patient should be included in the case series.

Table 17
Disease Primary Site of 159 Infants with Acute Lymphoid Leukemia from the SEER Database, 2008-2014

	N (%AL, 325)	*N* (% ALL, 159)	*N* (% C-ALL, 18)	*N* (% I-ALL, 141)
C42.1-bone marrow	147	147 (100%)	147 (100%)	147 (100%)

Note. A-ALL group, % of A-AL = 48.9%. C42.1 = ICD-O-3 code. A-ALL = all cases <12 months of acute lymphoid leukemia. C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months).

Diagnoses placed into the A-ALL group were first divided by C-ALL and I-ALL, then evaluated by the diagnostic confirmation methodology (see Table 18). The methodologies used for A-ALL included positive histology and immunophenotyping AND/OR positive genetic studies (32, 9.84%); positive exfoliative cytology, no positive histology (3, 0.92%); positive histology (116, 35.7%); positive laboratory test/marker study (4, 1.23%); and unknown source (4, 1.23%; see Table 18). The C-ALL group was not confirmed by clinical diagnosis only (**), but rather by positive histology and immunophenotyping AND/OR positive genetic studies (3, 16.7%); positive exfoliative cytology, no positive histology (1, 5.56%); and positive histology (12, 66.7%), positive laboratory test/marker study (1, 5.56%). The I-ALL group was confirmed by positive histology and immunophenotyping AND/OR positive genetic studies (29, 20.5%); positive exfoliative cytology, no positive histology (2, 1.42%); positive histology (104, 73.8%), positive laboratory test/marker study (3, 2.13%); and unknown source (3, 2.13%). The majority of clinical diagnoses of ALL were confirmed with only histology information, followed by cases, which used both positive histology and immunophenotyping AND/OR positive genetic studies to ensure the correct diagnoses.

Table 18
Diagnostic Confirmation Methodology of 159 Infants with Acute Lymphoid Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (% A-ALL, 159)	*N* (% C-ALL, 18)	*N* (% I-ALL, 141)
Clinical diagnosis only	**	**	**	**
Positive histology AND immunophenotyping AND/OR positive genetic studies	32 (9.84%)	32 (20.1%)	3 (16.7%)	29 (20.5 %)
Positive exfoliative cytology, no positive histology	3 (0.92%)	3 (1.89%)	1 (5.56%)	2 (1.42%)
Positive histology	116 (35.7%)	116 (73.0%)	12 (66.7%)	104 (73.8%)
Positive laboratory test/marker study	4 (1.23%)	4 (2.5%)	1 (5.56%)	3 (2.13%)
Unknown	4 (1.23%)	4 (2.5%)	1 (5.56%)	3 (2.13%)

Note. A-ALL group, % of A-AL = 48.9%. AL = acute leukemia. A-ALL = all cases <12 months of acute lymphoid leukemia. C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). **Null cases reported.

Diagnoses placed into the A-ALL group were first divided by C-ALL and I-ALL, then evaluated by insurance status. The insurance status for A-ALL included (a) any Medicaid (73, 22.4%), (b) insurance status unknown (4, 1.23%), (c) insured (68, 20.9%), (d) insured/no specifics (11, 3.38%), and (e) uninsured (3, 0.92%; see Table 20). The C-ALL group insurance status distribution included any Medicaid (8, 44.4%) and insured (19, 55.5%). The I-AML group included (a) any Medicaid (65, 46.1%), (b) insurance status unknown (4, 2.80%), (c) insured (58, 41.4%), (d) insured/no specifics (11, 7.81%), and (e) uninsured (3, 2.13%). The majority of patients diagnosed with ALL patients were insured either via private insurance or Medicaid.

Table 19
Insurance Status of 159 Infants with Acute Lymphoid Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (% A-ALL, 159)	*N* (% C-ALL, 18)	*N* (% I-ALL, 141)
Any Medicaid	73 (22.4%)	73 (45.9%)	8 (44.4%)	65 (46.1%)
Insurance status unknown	4 (1.23%)	4 (2.51%)	**	4 (2.80%)
Insured	68 (20.9%)	68 (42.7%)	10 (55.5%)	58 (41.1%)
Insured/no specifics	11 (3.38%)	11 (6.92%)	**	11 (7.81%)
Uninsured	3 (0.92%)	3 (1.88%)	**	3 (2.13%)

Note. A-ALL group, % of A-AL = 48.9%. AL = acute leukemia. A-ALL = all cases <12 months of acute lymphoid leukemia. C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). **Null cases reported.

Distinctive presentation of congenital and infant ALAL less than 12 months. The infants diagnosed with ambiguous lineage acute leukemia included those from birth to less than 2 months (C-ALAL), and those aged 2 months or greater to less than 12 months (I-ALAL) were evaluated in single group: all less than 12 months of age at diagnosis with ambiguous lineage acute leukemia. The A-ALAL group was evaluated for characteristics, including number of infants diagnosed birth to less than 2 months (C-ALAL), which included two diagnoses and aged 2 months or greater to less than 12 months (I-ALAL), which included 10 infants. The A-ALAL group included 12 infants, who were composed 3.69% of the 325 AL infant case series (see Table 20).

The C-ALAL group included two infants composed of 16.6% of the A-ALAL group and 0.62% of the AL case series, and the I-ALAL group included 10 infants composed of 83.3% of the A-ALAL group and 3.08% of the AL case series (see Table 20). The estimated age at

diagnosis in months calculated from months since last birthday was evaluated with a mean age of 5.6 months plus or minus *SD* 3.7 for infants diagnosed with ALAL. The A-ALAL group was evaluated for the sex of infants, and there were seven males (58.3%) and five females (41.7%) diagnosed. The A-ALAL group was evaluated for race of the infants: (a) Caucasian (White), (b) African American (Black), (c) Asian or Pacific Islander, (d) American Indian or Alaska Native, and (e) unknown race. The A-ALAL group ethnicity of the infants was designated as Hispanic or non-Hispanic. The race and ethnicity data included nine Caucasians (White), four Hispanic, and five non-Hispanic infants and three Asian or Pacific Islanders, 0 Hispanic, and three non-Hispanic infants. There were no African-American (Black), American Indian or Alaska Native, or unknown race infants (see Table 20).

Table 20
Demographic Profiles of 12 Infants with Ambiguous Lineage Acute Leukemia from the SEER Database, 2008-2014 in Leukemia Lineage Age Groups

Variables	*N* (A-AL %, 325)	C-ALAL, *N* (%A-ALAL; % AL)	I-ALAL, *N* (%A- ALAL; %AL)
Age	12 (3.69%)	2 (16.7%; 0.62%)	10 (83.3%; 3.08%)
Estimated age at diagnosis (months)	Mean ± *SD*	Median	
	5.6 ± 3.7	5.0	
Sex *N* (% A-ALAL)			
Male	7 (58.3%)	1 (50%)	6 (60.0%)
Female	5 (41.7%)	1 (50%)	4 (40.0%)
Race *N* (%)	Non-Hispanic (% race)	Hispanic (% race)	Total (race % of ALAL, *N* = 12)
Caucasian (White)	5 (55.5%)	4 (44.4%)	9 (75.0%)
C-ALAL	1	1	2
I- ALAL	4	3	7

(continued)

Variables	*N* (A-AL %, 325)	C-ALAL, *N* (%A-ALAL; % AL)	I-ALAL, *N* (%A- ALAL; %AL)
African-American (Black)	**	**	**
C-ALAL	**	**	**
I- ALAL	**	**	**
	N (A-AL %, 325)	C-ALAL, *N* (%A-ALAL; % AL)	I-ALAL, *N* (%A- ALAL; %AL)
Asian or Pacific Islander	3 (100%)	**	3 (100%)
C-ALAL	**	**	**
I- ALAL	3 (100%)	**	3 (100%)
American Indian or Alaska Native	**	**	**
C-ALAL	**	**	**
I- ALAL	**	**	**
Unknown	**	**	**
C-ALAL	**	**	**
I- ALAL	**	**	**

Note. AL = acute leukemia. A-ALAL = all cases <12 months of ambiguous lineage acute leukemia. C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). **Null cases reported.

The ALAL diagnoses were age stratified by leukemia type C-ALAL or I-ALAL. The C-ALAL group included two infants composed of 16.7% of the A-ALAL group and 0.62% of the AL case series. The I-ALAL group included 10 infants composed of 83.3% of the A-AML group and 3.08% of the AL case series (see Figure 15).

The estimated age at diagnosis distribution of the A-ALAL group was calculated from months since last birthday entered into the SEER registry. The majority of ALAL diagnoses (12) were distributed across five age groups: (a) C-ALAL in infants from birth to less than 1 month of age (2), I-ALAL in the infants aged 4 months or more to less than 5 months (2), 5 months or more to less than 6 months (2), age 7 months or more to less than 8 months (2), and 11 months or more to less than 12 months (2). Additional diagnoses included a single infant in the I-CALAL 3

months or more to less than 4 months, and 10 months or more to less than 11 months of age ([1], see Figure 16).

The A-ALAL diagnoses (12) were stratified by sex: male or female; there were no

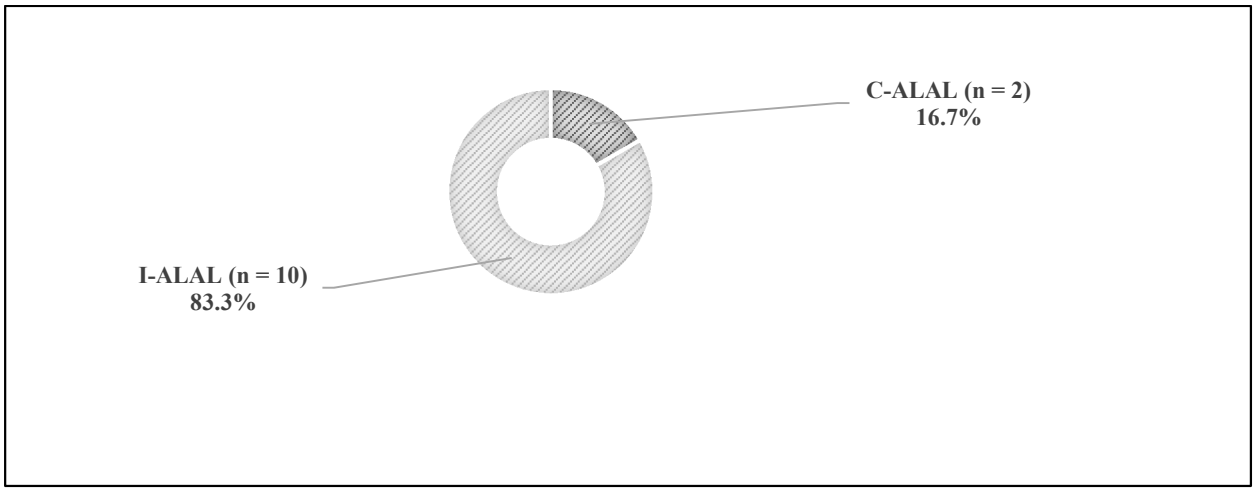


Figure 15. Age stratified leukemia type of ALAL infants less than 12 months. Age stratified leukemia groups of the cases retrieved from the SEER database from 2008-2014 diagnosed with ambiguous lineage acute leukemia. All infants from birth to < 2 months are placed into a congenital disease age group, and those age ≥ 2 months to < 12 months are placed into an infant age group. Subsequently, infants are placed into age stratified leukemia groups: C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months) and I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months).

diagnoses entered without a sex assigned to the SEER record (see Figure 17). The group was then assessed for the distribution of sex within the A-ALAL group. There were seven males composed 58.3% of the ALAL diagnoses. There were five females composed 41.7% of the ALAL diagnoses.

The A-ALAL diagnoses (12) were stratified by race and ethnicity of the infants: (a) Caucasian (White), (b) African-American (Black), (c) Asian or Pacific Islander, (d) American Indian or Alaska Native and (e) unknown race. Ethnicity included Hispanic or non-Hispanic infants (see Figure 18). The highest number of diagnoses occurred in non-Hispanic Caucasian

(White [5]) and the second largest number of diagnoses in Hispanic Caucasian (White [4]) infants.

Diagnoses in the combined American Indian or Alaskan Native race were the only other race in this group with the majority as non-Hispanic infants (3). There were no diagnoses in African-American (Black) or combined Asian or Pacific Islander race group. There were no diagnoses placed into the unknown race category.

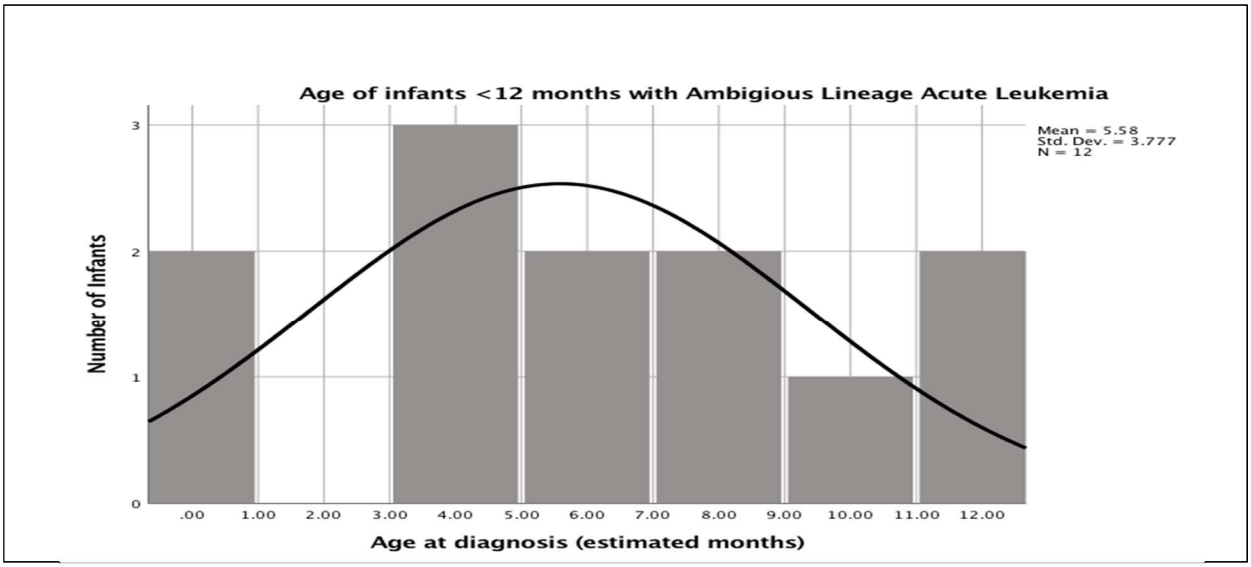


Figure 16. Ambiguous lineage acute leukemia age distribution. Age at diagnosis with ambiguous lineage acute leukemia for 12 infants (< 12 months of age) from the SEER database, 2008-2014. Estimated age at diagnosis in months is calculated from months since last birthday derived from month of diagnosis subtracted from birth month as entered into SEER.

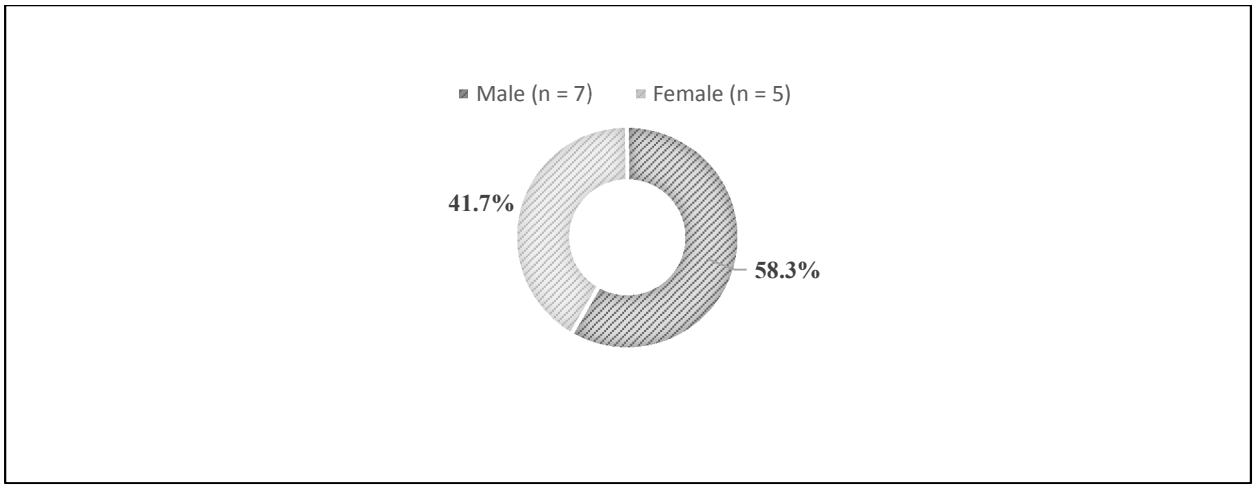
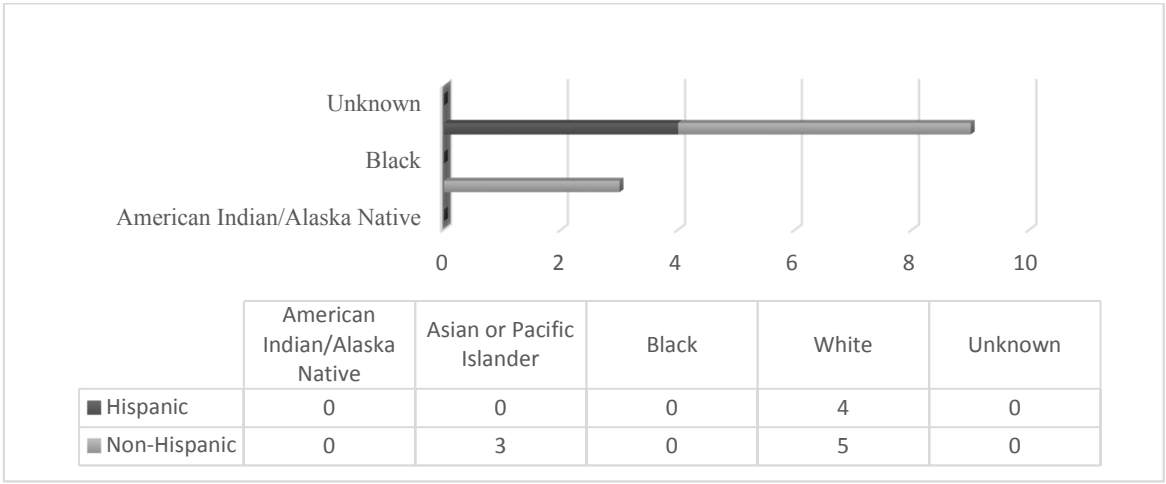


Figure 17. Sex of infants less than12 months with ambiguous lineage acute leukemia. Sex distribution for 12 infants (< 12 months of age) diagnosed with ambiguous lineage acute leukemia from the SEER database, 2008-2014.

Diagnoses placed into the A-ALAL group were first divided by C- ALAL and I-ALAL were then evaluated by the designated ICD-O-3/WHO 2017 aligned leukemia group acute myeloid leukemia and related neoplasms and further defined by a single subgroup and



	American Indian/Alaska Native	Asian or Pacific Islander	Black	White	Unknown
Hispanic	0	0	0	4	0
Non-Hispanic	0	3	0	5	0

Figure 18. Race and ethnicity of infants less than 12 months with ambiguous lineage acute leukemia. Race and ethnicity of 12 infants (< 12 months of age) diagnosed with ambiguous lineage acute leukemia from the SEER database, 2008-2014.

subtypes (see Table 21, Figure 19). All infant diagnoses designated A-ALAL (12 diagnoses, 3.70% of AL) were placed into the acute myeloid leukemia and related neoplasms group and

subsequently placed into ambiguous lineage acute leukemia (subgroup). The ambiguous lineage acute leukemia subgroup was divided into acute undifferentiated leukemia (subtype); "mixed phenotype acute leukemia with t(9;22)(q34.1;11.2); *BCR-ABL1* (subtype);" "mixed phenotype acute leukemia with t(v;11q23.3); *KMT2A* rearranged (subtype);" mixed phenotype acute leukemia with B/myeloid, NOS (subtype); and mixed

Table 21
Available WHO 2017 Classification of Ambiguous Lineage Acute Leukemia of 12 infants by Age Stratified Groups from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (% of A-ALAL, 12)	*N* (% of C-ALAL, 2)	*N* (% of I-ALAL, 10)
Acute undifferentiated leukemia	3 (0.92%)	3 (25.0%)	1 (8.33%)	2 (16.6 %)
Mixed phenotype acute leukemia with t(9;22)(q34.1;11.2); *BCR-ABL1*	**	**	**	**
Mixed phenotype acute leukemia with t(v;11q23); *KMT2A*(MLL) rearranged	3 (0.92%)	3 (25.0%)	1 (8.33%)	2 (16.6 %)
Mixed phenotype acute leukemia, B/myeloid, NOS	4 (1.23%)	4 (33.0%)	**	4 (33.3 %)
Mixed phenotype acute leukemia, T/myeloid, NOS	2 (0.62%)	2 (16.7%)	**	4 (33.3 %)

Note. Ambiguous lineage acute leukemia group, % of A-AL = 3.69%. AL = acute leukemia; A-ALAL = all cases < 12 months of ambiguous lineage acute leukemia; C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). **Null cases reported in this subtype.

phenotype acute leukemia acute leukemia with T/myeloid, NOS (subtype). The mixed phenotype acute leukemia with b/myeloid, NOS was diagnosed in four infants. Acute undifferentiated leukemia and "mixed phenotype acute leukemia with t(v;11q23.3); *KMT2A* rearranged" were diagnosed in three infants, respectively. Mixed phenotype acute leukemia with T/myeloid, NOS was diagnosed in two infants in the case series. There were no diagnoses of "mixed phenotype acute leukemia with t(9;22)(q34.1;11.2); *BCR-ABL1"* in the case series. The majority of infants in the A-ALAL group were diagnosed with mixed phenotype acute leukemia with B/myeloid,

NOS (4, 33.3% of A-ALAL, 1.23% of AL) and the fewest with mixed phenotype acute leukemia with T/myeloid, NOS (2, 16.7% of A- ALAL, 0.62% of AL).

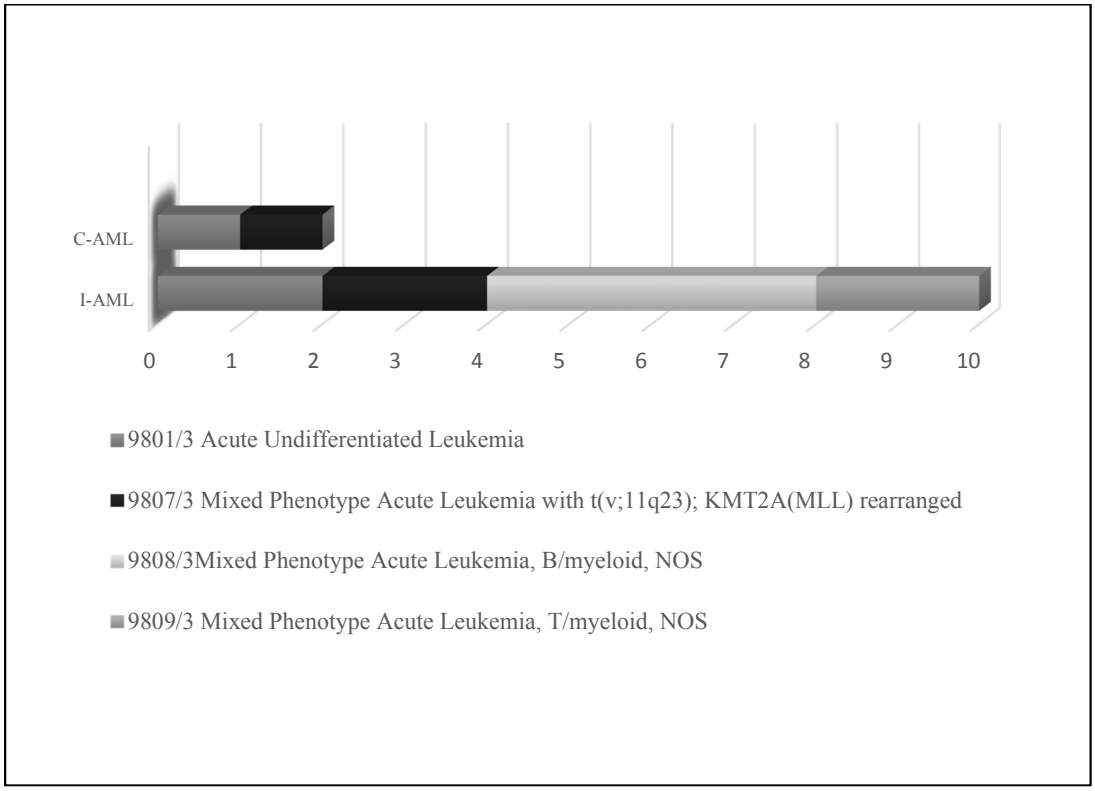


Figure 19. WHO ALAL 2017 subtypes in infants less than 12 months of age at diagnosis. WHO ALAL 2017 subtypes of 12 infants under 12 months of age at diagnosis from the SEER database, 2008-2014.

Epidemiological data. Diagnoses placed into the A-ALAL group were first divided by C-ALAL and I-ALAL, then evaluated by the registry reporting source. The registry reporting sources for A-ALAL included hospital inpatient/outpatient or clinic (11, 3.39%) and laboratory only (hospital or private; 1, 0.31%; see Table 22). The C-ALAL group was equally reported by hospital inpatient/outpatient or clinic (1, 50.0%) and laboratory only (hospital or private; 1, 50.0%) and the in the I-ALAL group, the majority of cases were reported by hospital inpatient/outpatient or clinic (10). The majority of clinical diagnoses of ALAL occur in a hospital inpatient/outpatient or clinic environment.

Table 22
Registry Reporting Source of 12 Infants with Ambiguous Lineage Acute Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%A-ALAL, 12)	*N* (% of C-ALAL, 2)	*N* (% of I-ALAL, 10)
Hospital inpatient/outpatient or clinic	11 (3.39%)	11(91.7%)	1 (50.0%)	10 (100%)
Laboratory only (hospital or private)	1 (0.31%)	1 (8.33%)	1 (50.0%)	**

Note. Ambiguous lineage acute leukemia group, % of A-AL = 3.69%. AL = acute leukemia. A-ALAL = all cases < 12 months of ambiguous lineage acute leukemia. C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). **Null cases reported.

Diagnoses placed into the A-ALAL group were first divided by C-ALAL and I-ALAL, then evaluated by the disease primary site. The disease primary site as anticipated for all patients was the bone marrow (see Table 23). As leukemia are clonal hematopoietic stem cells disorders generally defined by the presence of 20% or more bone marrow involvement, the primary site of disease serves as an internal control that the appropriate diagnoses have been assigned and the patient should be included in the case series.

Table 23
Disease Primary Site of 12 Infants with Ambiguous Lineage Acute Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%A-ALAL, 12)	*N* (% of C-ALAL, 2)	*N* (% of I-ALAL, 10)
C42.1-Bone Marrow	12 (34.5%)	12 (100%)	12 (100%)	12 (100%)

Note. Ambiguous lineage acute leukemia group, % of A-AL = 3.69%. C42.1 = ICD-O-3 code. A-ALAL = all cases < 12 months of ambiguous lineage acute leukemia. AL = acute leukemia. C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months).

Diagnoses placed into the A-ALAL group were first divided by C-ALAL and I-ALAL, then evaluated by the diagnostic confirmation methodology. The methodologies used for A-ALAL included positive histology and immunophenotyping AND/OR positive genetic studies (2, 0.62%) and positive histology (10, 3.08%; see Table 24). The C-ALAL group was equally confirmed by positive histology and immunophenotyping AND/OR positive genetic studies (1, 50.0%) and positive histology (1, 50.0%), and the I-ALAL group confirmed by positive histology and immunophenotyping AND/OR positive genetic studies (1, 10.0%) and positive histology (9, 90.0%). The majority of clinical diagnoses of ALAL were confirmed with only histology information, followed by cases confirmed with both positive histology and immunophenotyping AND/OR positive genetic studies to ensure the correct diagnoses.

Table 24
Diagnostic Confirmation Methodology of 12 Infants with Ambiguous Lineage Acute Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%A-ALAL, 12)	*N* (% of C-ALAL, 2)	*N* (% of I-ALAL, 10)
Clinical diagnosis only	**	**	**	**
Positive histology AND immunophenotyping AND/OR positive genetic studies	2 (0.62%)	2 (17.0%)	1 (50.0%)	1 (10.0%)
Positive exfoliative cytology, no positive histology	**	**	**	**
Positive histology	10 (3.08%)	10 (83.0%)	1 (50.0%)	9 (90.0%)
Positive laboratory test/marker study	**	**	**	**
Unknown	**	**	**	**

Note. Ambiguous lineage acute leukemia group, % of A-AL = 3.69%. AL = acute leukemia. A-ALAL = all cases < 12 months of ambiguous lineage acute leukemia. C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). **Null cases reported in this subtype.

Diagnoses placed into the A-ALAL group were first divided by C-ALAL and I-ALAL, then evaluated by insurance status. The insurance status included (a) any Medicaid (1, 0.31%); (b) insurance status unknown (1, 0.31%), (c) insured (9, 2.77%), and (d) uninsured (1, 0.31%; see Table 25). The C-ALAL group insurance status distribution included only (a) insured (2, 100.0%), the I-ALAL group with any Medicaid (1, 10.0%); (b) insurance status unknown (1, 10.0%); (c) insured (7, 30.0%); (d) uninsured (1, 10.0%). The majority of patients diagnosed with ALAL patients were insured with private insurance.

Table 25
Insurance Status of 12 Infants with Ambiguous Lineage Acute Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%A-ALAL, 12)	*N* (% of C-ALAL, 2)	*N* (% of I-ALAL, 10)
Any Medicaid	1 (0.31%)	1 (8.33%)	**	1 (10.0%)
Insurance status unknown	1 (0.31%)	1 (8.33%)	**	1 (10.0%)
Insured	9 (2.77%)	9 (75.0%)	2 (100%)	7 (30.0%)
Insured/no specifics	**	**	**	**
Uninsured	1 (0.31%)	1 (8.33%)	**	1 (10.0%)

Note. Ambiguous lineage acute leukemia group, % of A-AL=3.69%. AL = acute leukemia. A-ALAL = all cases < 12 months of ambiguous lineage acute leukemia. C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). **Null cases reported.

Distinctive presentation of congenital and infant OAL less than 12 months. The infants diagnosed with other acute leukemia, included those from birth to less than 2 months (C-OAL), and those aged 2 months or more to less than 12 months (I-OAL) were evaluated in single group. All less than 12 months of age at diagnosis with other acute leukemia (A-OAL). The A-OAL group was evaluated for characteristics, including number of infants diagnosed birth to less than

2 months (C-OAL) with five diagnoses and 2 months or more to less than 12 months (I-OAL) with two. The A-OAL group included seven infants, which were composed 2.15% of the 325 AL infant case series (see Figure 2, Table 26).

The C-OAL group included five infants composed 71.4% of the A-OAL group and 1.53% of the AL case series, and the I-OAL group included two infants composed of 28.5% of the A-OAL group and 0.61% of the AL case series (see Figure 2). The estimated age at diagnosis in months calculated from months since last birthday was evaluated with a mean age of 1.1 months plus or minus *SD* 1.5 for infants diagnosed with OAL (see Table 26). The A-OAL group was evaluated for the sex of infants. There were three males (42.9%) and four females (57.1%) diagnosed. The A-OAL group was evaluated for race of the infants: (a) Caucasian (White), (b) African-American (Black), (c) Asian or Pacific Islander, (d) American Indian or Alaska Native, and (e) unknown race. The A-OAL group was evaluated for ethnicity of the infants: Hispanic and non-Hispanic. The race and ethnicity data included (a) five Caucasian (White), three Hispanic, and two non-Hispanic infants; (b) one African-American (Black) non-Hispanic infant; and (c) one Asian or Pacific Islander non-Hispanic infant. There were no American Indian or Alaska Native or unknown race designated infants in the A-OAL group (see Table 26).

Table 26
Demographic Profiles of Seven Infants with Other Acute Leukemia from the SEER Database, 2008-2014 for Leukemia Lineage Age Groups

	N (A-AL %, 325)	C-OAL, *N* (% A-OAL; % AL)	I- OAL, *N* (% A-OAL; %AL)
Age	7 (2.15%)	5 (71.4%; 1.53%)	2 (28.5%; 0.61%)
Estimated age at diagnosis (months)	Mean ± *SD*	Median	
	1.1 ± 1.5	1.0	
Sex *N* (% A-OAL)			
Male	3 (42.9%)	2 (40.0%)	1 (50.0%)
Female	4 (57.1%)	3 (60.0%)	1 (50.0%)
Race *N* (%)	Non-Hispanic (% race)	Hispanic (% race)	Total (race % of OAL, *N* = 7)
Caucasian (White)	2 (40.0%)	3 (60.0%)	5 (71.4%)
C-OAL	2 (50.0%)	2 (50.0%)	4 (57.1%)
I- OAL	**	1 (100%)	1 (14.3%)
African American (Black)	1 (100%)	**	1 (14.3%)
C-OAL	**	**	**
I- OAL	1 (100%)	**	1 (14.3%)
Asian or Pacific Islander	1 (100%)	**	1 (14.3%)
C-OAL	1 (100%)	**	1 (14.3%)
I- OAL	**	**	**
American Indian or Alaska Native	**	**	**
C-OAL	**	**	**
I- OAL	**	**	**
Unknown	**	**	**
C-OAL	**	**	**
I- OAL	**	**	**

Note. AL = acute leukemia. A-OAL = all cases < 12 months of congenital other acute leukemia. C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). **Null cases reported.

The OAL diagnoses were age stratified by leukemia type: C-OAL or I-OAL. The C-OAL group included five infants composed of 71.4% of the A-OAL group and 1.53% of the AL case series. The I-OAL group included two infants composed of 28.6% of the A-OAL group and 0.61% of the AL case series (see Figure 20).

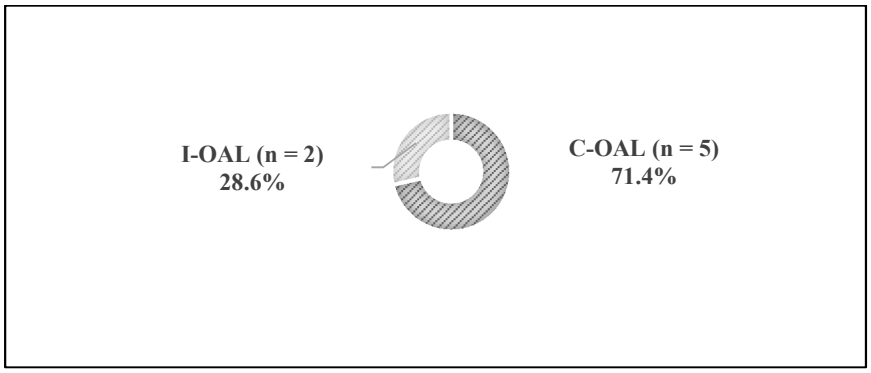


Figure 20. Age stratified leukemia type of OAL infants less than 12 months. Age stratified leukemia groups of the cases retrieved from the SEER database from 2008-2014, diagnosed with other acute leukemia. C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months).

The estimated age at diagnosis distribution of the A-OAL group was calculated from months since last birthday entered into the SEER registry. The majority of OAL diagnoses (3) occurred in the C-OAL in the infants from birth to less than 1 month of age (see Figure 21). In addition, the other age of diagnoses (2) with acute leukemia within the case series occurred in patients from 1 month or more to less than 2 months. Additional diagnoses include 1 infant diagnosed from greater than or equal to 2 to less than 3 months, and greater than or equal to 4 to less than 5 months, respectively.

The A-OAL diagnoses (7) were stratified by sex: male or female; there were no diagnoses entered without a sex assigned to the SEER record (see Figure 22). The group was then assessed for the distribution of sex within the A-OAL group. There were 3 males, that is, males composed 43% of the OAL diagnoses. There were four females composed of 57% of the ALAL diagnoses.

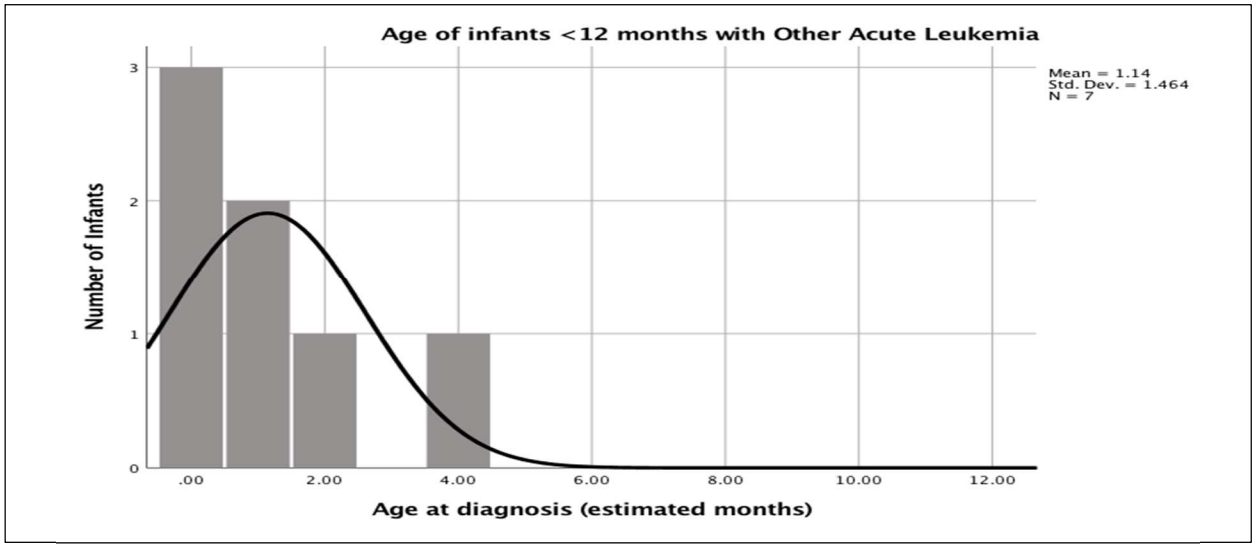


Figure 21. Other acute leukemia age distribution. Age at diagnosis with other leukemia for 147 infants (< 12 months of age) from the SEER database, 2008-2014. Estimated age at diagnosis in months is calculated from months since last birthday derived from month of diagnosis subtracted from birth month as entered into SEER.

The A-OAL diagnoses (7) were stratified by race and ethnicity of the infants: (a) Caucasian (White), (b) African-American (Black), (c) Asian or Pacific Islander, (d) American Indian or Alaska Native, and (e) unknown race. Ethnicity included Hispanic or non-Hispanic infants (see Figure 22). The highest number of diagnoses occurred in Hispanic Caucasian (White) infants (3), and the second largest number of diagnoses was in in non-Hispanic Caucasian (White) infants (2). The combined Asian or Pacific Islander had a single non-Hispanic infant diagnosis. The African-American (Black) race group had a single non-Hispanic infant diagnosis. There were no diagnoses in the combined American Indian/Alaska Native race group. There were no diagnoses placed into the unknown race category.

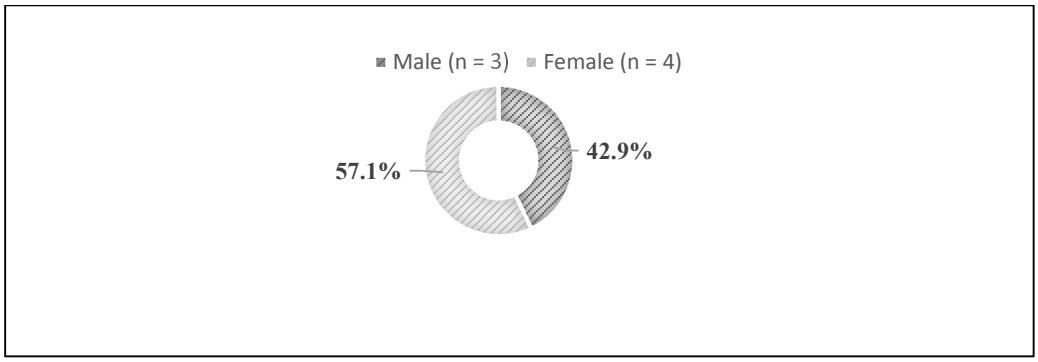
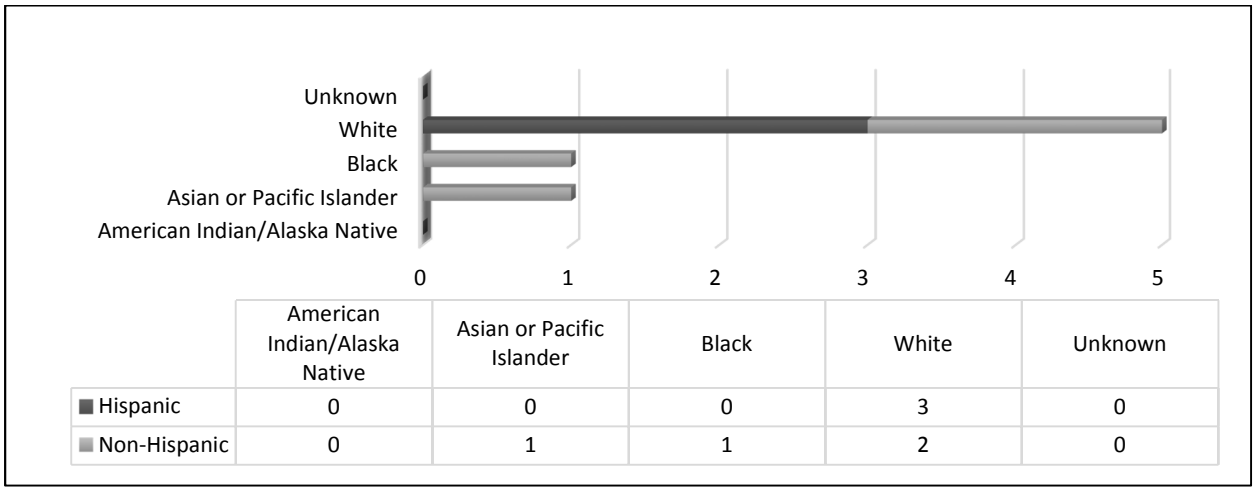


Figure 22. Sex of infants less than 12 months with other acute leukemia. Sex distribution for seven infants (< 12 months of age) diagnosed with other acute leukemia from the SEER database, 2008-2014.



	American Indian/Alaska Native	Asian or Pacific Islander	Black	White	Unknown
Hispanic	0	0	0	3	0
Non-Hispanic	0	1	1	2	0

Figure 23. Race and ethnicity of infants with other acute leukemia under 12 months. Race and ethnicity of seven infants (< 12 months of age) diagnosed with other acute leukemia from the SEER database, 2008-2014.

Diagnoses placed into the A-OAL group were first divided by C-OAL and I-OAL, then evaluated by the designated ICD-O-3/WHO 2017 aligned leukemia group acute myeloid leukemia and related neoplasms and further defined by a single subgroups/subtype. All infant diagnoses from the acute myeloid leukemia and related neoplasms group were divided into acute leukemia, NOS (subgroup, subtype; see Table 27). This subgroup/subtype could not be further subdivided by additional ICD-O-3/WHO 2017 aligned subtypes given the NOS category

indicates the lack of other identifying characteristics given the diagnosis. Within the AL NOS subgroup/subtype, the seven diagnoses composed 21.5% of AL case series (see Table 27).

Table 27
Available WHO 2017 Classification of Other Acute Leukemia of Seven Infants by Age Stratified Groups from the SEER Database, 2008-2014

	N (%A- AL, 325)	*N* (%A-OAL, 7)	*N* (% of C-OAL, 5)	*N* (% of I-OAL, 2)
Acute leukemia, NOS (Subgroup, Subtype)	7 (2.15%)	7 (100%)	5 (100%)	2 (100%)

Note. Other acute leukemia group, % of A-AL = 2.15%. AL = acute leukemia. A-OAL = all cases < 12 months of congenital other acute leukemia. C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months).

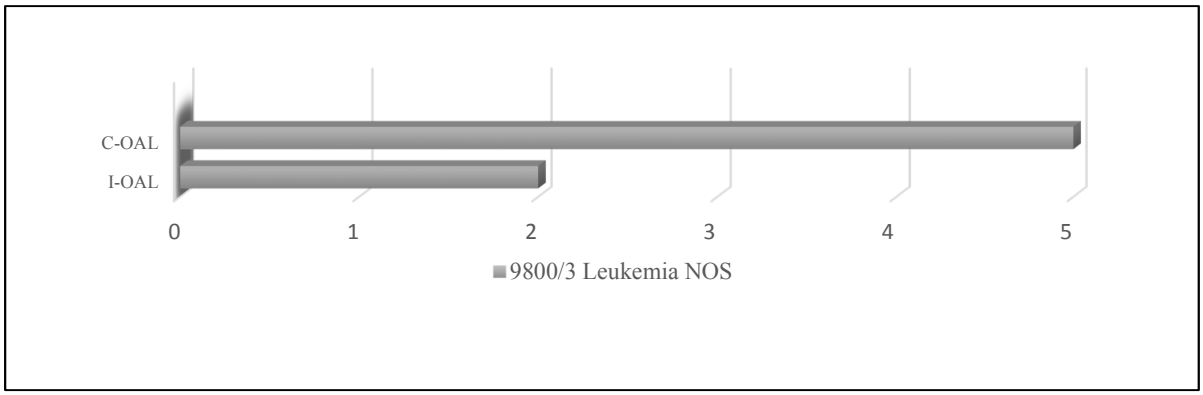


Figure 24. WHO OAL 2017 subtypes in infants under 12 months of age at diagnosis. WHO OAL 2017 subtype of seven infants < 12 months of age at diagnosis from the SEER database, 2008-2014.

Epidemiological data. Diagnoses placed into the A-OAL group were first divided by C-OAL and I-OAL, then evaluated by the registry reporting source. The registry reporting sources for A-OAL included hospital inpatient/outpatient or clinic (5, 1.53%), autopsy only (1, 0.31%), and physician office/private medical practitioner (1, 0.31%; see Table 28). The C-OAL group was reported by hospital inpatient/outpatient or clinic (4, 80.0%) and physician's office/private medical practitioner (1, 20.0%), and the I-OAL group reported by hospital inpatient/outpatient or

clinic (1, 50.0%) and autopsy only (1, 50.0%). The majority of clinical diagnoses of OAL occur in a hospital inpatient/outpatient or clinic environment.

Table 28
Registry Reporting Source of Seven Infants with Other Acute Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%A-OAL, 7)	*N* (% of C-OAL, 5)	*N* (% of I-OAL, 2)
Hospital inpatient/outpatient or clinic	5 (1.53%)	5 (71.4%)	4 (80.0%)	1 (50.0 %)
Laboratory only (hospital or private)	**	**	**	**
Autopsy only	1 (0.31%)	1 (14.3%)		1 (50.0 %)
Physician's office/private medical practitioner (LMD)	1 (0.31%)	1 (14.3%)	1 (20.0%)	**

Note. Other acute leukemia group, % of A-AL = 2.15%. AL = acute leukemia. A-OAL = all cases <12 months of congenital other acute leukemia. C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). **Null cases reported. LMD = laboratory medical directorship.

Diagnoses placed into the A-OAL group were first divided by C-OAL and I-OAL, then evaluated by the disease primary site. The disease primary site as anticipated for all patients was the bone marrow (see Table 29). As leukemia are clonal hematopoietic stem cells disorders generally defined by the presence of 20% or more bone marrow involvement, the primary site of disease serves as an internal control that the appropriate diagnoses have been assigned and the patient should be included in the case series.

Table 29
Disease Primary Site of Seven Infants with Other Acute Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%A-OAL, 7)	*N* (% of C-OAL, 5)	*N* (% of I-OAL, 2)
C42.1-bone marrow	7 (2.15%)	7 (100%)	5 (100%)	2 (100%)

Note. Other acute leukemia group, % of A-AL = 2.15%. C42.1 = ICD-O-3 code. A-OAL = all cases < 12 months of other acute leukemia. AL = acute leukemia. C-ALAL = congenital ambiguous lineage acute leukemia.

Diagnoses placed into the A-OAL group were first divided by C-OAL and I-OAL, then evaluated by the diagnostic confirmation methodology. The methodologies used for A-OAL included positive histology (4, 1.23%), positive laboratory test/marker study (1, 0.31%), and unknown source (2, 0.62%; see Table 31). The C-OAL group was confirmed by positive histology (2, 40.0%), positive laboratory test/marker study (1, 20.0%), and unknown source (2, 40.0%), and the I-OAL group was confirmed by positive histology (2, 100.0%) only. There were no diagnoses confirmed via clinical diagnosis only; positive histology and immunophenotyping AND/OR positive genetic studies; or positive exfoliative cytology, no positive histology. The majority of clinical diagnoses of OAL were confirmed with only histology information, followed by cases that used an unknown methodology to conclude the diagnoses.

Table 30
Diagnostic Confirmation Methodology of Seven Infants with Other Acute Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (% A-OAL, 7)	*N* (% of C-OAL, 5)	*N* (% of I-OAL, 2)
Clinical diagnosis only	**	**	**	**
Positive histology AND immunophenotyping AND/OR positive genetic studies	**	**	**	**
Positive exfoliative cytology, no positive histology	**	**	**	**
Positive histology	4 (1.23%)	4 (57.1%)	2 (40.0%)	2 (100%)
Positive laboratory test/marker study	1 (0.31%)	1 (14.3%)	1 (20.0%)	**
Unknown	2 (0.62%)	2 (28.6%)	2 (40.0%)	**

Note. Other acute leukemia group, % of A-AL = 2.15%. AL = acute leukemia. A-OAL = all cases <12 months of congenital other acute leukemia. C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). **Null cases reported.

Diagnoses placed into the A-OAL group were first divided by C-OAL and I-OAL, then evaluated by insurance status. The insurance status included any Medicaid (2, 0.62%), insurance status unknown (4, 1.23%), and insured/no specifics (1, 0.31%; see Table 31). The C-OAL group insurance status distribution included any Medicaid (1, 20.0%), insurance status unknown (3, 60.0%), and insured/no specifics (1, 20.0%). The I-OAL group included any Medicaid (1, 50.0%) and insurance status unknown (1, 50.0%). The majority of patients diagnosed with OAL patients had an insurance status unknown at diagnosis.

Table 31
Insurance Status of Seven Infants with Other Acute Leukemia from the SEER Database, 2008-2014

	N (%A-AL, 325)	*N* (%A-OAL, 7)	*N* (% of C-OAL, 5)	*N* (% of I-OAL, 2)
Any Medicaid	2 (0.62%)	2 (28.6%)	1 (20.0%)	1 (50.0%)
Insurance status unknown	4 (1.23%)	4 (57.1%)	3 (60.0%)	1 (50.0%)
Insured	**	**	**	**
Insured/no specifics	1 (0.31%)	1 (14.3%)	1 (20.0%)	**
Uninsured	**	**	**	**

Note. Other acute leukemia group, % of A-AL = 2.15%. AL = acute leukemia. A-OAL = all cases < 12 months of congenital other acute leukemia. C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). **Null cases reported.

Research Question 1.1. "Are there distinctive clinical presentations of children diagnosed with congenital AML and ALL at 1 and 2 months of age?" To address Research Question 1.1, the designated congenital acute leukemia (C-AL) infants diagnosed with acute leukemia were divided into AML, ALL, ALAL, or OAL, given not all infant acute leukemia retrieved from the SEER registry are consistent with the two distinct lineages myeloid (AML), lymphoid (ALL) but also acute leukemia of ambiguous lineage and an "other" category for uncategorized other acute leukemia. The AML, ALL, ALAL, and OAL groups were subsequently divided by estimated age at diagnosis birth to less than 2 months (C-AML, C-ALL, C-ALAL, and C-OAL; see Table 32). The C-AML, C-ALL, C-ALAL, and C-OAL groups were divided into estimated age at diagnosis from birth to less than 1 month ($C\text{-}AML^{B\text{-}1}$, $C\text{-}ALL^{B\text{-}1}$, $C\text{-}ALAL^{B\text{-}1}$, and $C\text{-}OAL^{B\text{-}1}$) and 1 one month or more to less than 2 months ($C\text{-}AML^{1\text{-}2}$, $C\text{-}ALL^{1\text{-}2}$, $C\text{-}ALAL^{1\text{-}2}$, and $C\text{-}OAL^{1\text{-}2}$). The question was addressed using descriptive statistics of the mean, median, and standard deviation for each disease pathology variable (see Table 32). The chi-

square test was used to evaluate the differences between the disease and age groups; the null hypothesis of the test was that the age of diagnosis would not be significantly related to the type of leukemia diagnosed. An evaluation of age in months versus leukemia subtype using the chi-square test = $X^2 = 383.83$, $p < .05$. These findings are expected as these are age stratified groups, including C-AML, C-ALL, C-ALAL, and C-OAL. An evaluation of age in months versus leukemia lineage type (myeloid, lymphoid, mixed lineage, or other) using the chi-square test =$X^2 = 31.806$, $p = .095$. The finding is approaching significance as expected based on previous epidemiology data that suggested ALL occurs at a higher frequency in older infants versus AML that occurs at a higher frequency in young infants.

Table 32
Demographic Profiles of Age and Sex of 59 Infants with Congenital Leukemia from the SEER Database, 2008-2014 for Leukemia Lineage Age Groups

	(A-AL %)	C-AML, *N* (% of C-AL)	C-ALL, *N* (% of C-AL)	C-ALAL, *N* (% of C-AL)	C-OAL, *N* (% of C-AL)
N	59 (18.1%)	34 (57.6%)	18 (30.5%)	2 (3.4%)	5 (8.47%)
Age					
Estimated at diagnosis (months) (Mean ± *SD*)	0.37 ± 0.49	0.29 ± 0.46	0.55 ± 0.51	0.00 (Birth)	0.40 ± 0.54
Sex *N* (%)					
Male	26 (8.0%)	17 (50%)	6 (33.3%)	1 (50%)	2 (40.0%)
Female	33 (10.2%)	17 (50%)	12 (66.7%)	1 (50%)	3 (60.0%)

Note. $N = 325$. Chi square ($\alpha = .05$)**.** Age in months vs. leukemia subgroup $X^2 = 383.83$, $p = <.05$. Age in months vs. leukemia lineage $X^2 = 31.806$, $p = .095$. AL = acute leukemia. C-AML = congenital acute myeloid leukemia (birth to < 2 months). C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months; C-OAL = congenital other acute leukemia (birth to < 2 months).

To further address research question 1.1, the demographic profiles of race and ethnicity of 59 infants with congenital leukemia were evaluated. The C-AL group was evaluated for race of the infants: (a) Caucasian (White), (b) African-American (Black), (c) Asian or Pacific Islander, (d) American Indian or Alaska Native and (e) unknown race; the ethnicity of the infants was evaluated as Hispanic or non-Hispanic. The C-AL group was first divided into C-AML, C-ALL, C-ALAL, or C-OAL. The race and ethnicity data included (a) 44 Caucasians (White); 25 Hispanic and 19 non-Hispanic infants composed of C-AML (22, 64.7% of C-AML), C-ALL (16, 88.9% of C-ALL), C-ALAL (2, 100% of C-ALAL), and C-OAL (4, 80% of C-OAL); (b) 4 African-American (Black) non-Hispanic infants composed of C-AML (4, 11.8% of C-AML); (c) nine Asian or Pacific Islander, one Hispanic, and eight non-Hispanic composed of C-AML (6, 17.6% of C-AML), C-ALL (2, 11.1% of C-ALL), and C-OAL (1, 20.% of C-OAL). There were no American Indian or Alaska Native or unknown race designated infants in the C-AL group (see Table 33).

Table 33

Demographic Profiles of Race and Ethnicity of 59 Infants with Congenital Leukemia from the SEER Database, 2008-2014 for Leukemia Lineage Age Groups

Race and Ethnicity						
	C-AML			C-ALL		
	Non-Hispanic *N* (% race)	Hispanic *N* (% race)	Total *N* (race % C-AML)	Non-Hispanic, *N* (% race)	Hispanic *N* (% race)	Total *N* (race % C-ALL)
Caucasian (White)	8 (36.4%)	14 (41.2%)	22 (64.7%)	8 (50.0%)	8 (50.0%)	16 (88.9%)
African-American (Black)	4 (100%)	**	4 (11.8%)	**	**	**
Asian or Pacific Islander	6 (100%)	**	6 (17.6%)	1 (50.0%)	1 (50.0%)	2 (11.1%)
American Indian or Alaska Native	**	**	**	**	**	**
Unknown	2 (100%)	**	2 (5.88%)	**	**	**
	C-ALAL			C-OAL		
	Non-Hispanic *N* (% race)	Hispanic *N* (% race)	Total *N* (race % C-ALAL)	Non-Hispanic N(% race)	Hispanic N (% race)	Total N (race % C-OAL)
Caucasian (White)	1 (50%)	1 (50%)	2 (100%)	2 (50.0%)	2 (50.0%)	4 (80.0%)
African-American (Black)	**	**	**	**	**	**
Asian or Pacific Islander	**	**	**	1 (100%)	**	1 (20.0%)
American Indian or Alaska Native	**	**	**	**	**	**
Unknown	**	**	**	**	**	**

Note. C-AML *N* = 34. C-ALL *N* = 18. C-ALAL *N* = 2. C-OAL *N* = 5. C-AL = all congenital acute leukemia diagnoses. C-AML = congenital acute myeloid leukemia (birth to < 2 months). C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). C-OAL = congenital other acute leukemia (birth to < 2 months). **Null cases reported.

To further address Research Question 1.1, the age group profiles of 59 infants with congenital leukemia were evaluated. The congenital leukemia group divided by age of diagnosis birth to less than 1 (C-AL^{B-1}) and 1 month or more to less than 2 months (C-AL$^{1-2}$) without regard to ICD-O-3/WHO 2017 subtypes. The C-AL^{B-1} included 22 diagnoses (37.3% of C-AL), and the C-AL$^{1-2}$ included 37 diagnoses (62.7% of C-AL). A larger number of leukemia diagnoses occurred from birth to under 1 month of age (37) with the children aged 1 to 2 months accounting for the remaining diagnoses ([22], see Figure 25).

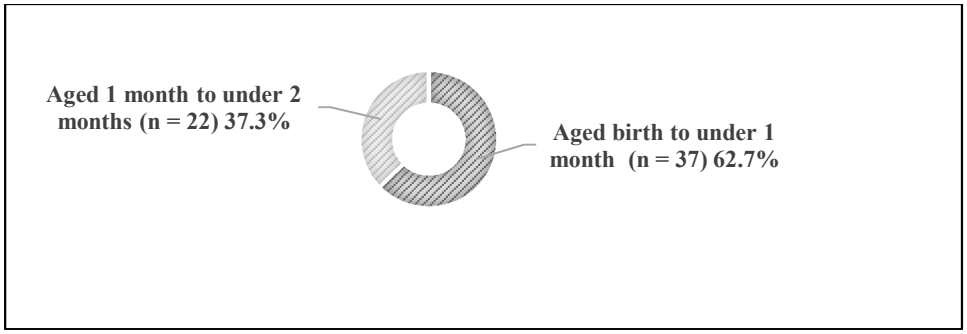


Figure 25. Age stratified groups of congenital leukemia. Age stratified groups of congenital leukemia of 59 infants under 2 months of age at diagnosis from the SEER database, 2008-2014.

Research Question 2.1. "What is the proportion of congenital AML and ALL in 1 to 2-month-old infants?" To address Research Question 2.1, the infants diagnosed with acute leukemia were divided into AML, ALL, ALAL, or OAL, given not all infant acute leukemia retrieved from the SEER registry are consistent with the two distinct lineages myeloid (AML) and lymphoid (ALL) but also acute leukemia of ambiguous lineage and an "other" category for uncategorized other acute leukemia. The AML, ALL, ALAL, and OAL groups were subsequently divided by estimated age at diagnosis birth to less than 2 months (C-AML, C-ALL, C-ALAL, and C-OAL). The C-AML, C-ALL, C-ALAL, and C-OAL groups were divided into estimated age at diagnosis from birth to less than 1 month (C-AML^{B-1}, C-ALL^{B-1}, C-ALAL^{B-1}, and C-OAL^{B-1}) and greater than or equal to 1 month or more to less than 2 months (C-AML$^{1-2}$,

C-ALL[1-2], C-ALAL[1-2], and C-OAL[1-2]). The question was addressed using descriptive statistics of age group (see Table 34). The chi-square test was used to evaluate the association between the age at diagnoses and C-AL type. An evaluation of age at diagnoses and C-AL type were made using the chi-square test =$X^2 = 4.676$, $p = .197$. There was no statistically significant relationship between age at diagnoses and C-AL type, meaning C-AML, C-ALL, C-ALAL, and C-OAL are equally likely to be diagnosed in both C-AL[B-1] and C-AL[1-2] groups. A larger number of leukemia diagnoses occurred from birth to under 1 month of age (38, 11.7% of C-AL), and the remaining diagnoses were in children aged 1 to 2 months (21, 6.4% of C-AL).

Table 34
The Leukemia Lineage of 59 Infants with Congenital Leukemia from the SEER Database, 2008-2014 for Leukemia Lineage Age Groups

	(A-AL %), 325	C-AML (% of C-AL)	C-ALL (% of C-AL)	C-ALAL (% of C-AL)	C-OAL (% of C-AL)
	59 (18.1%)	34 (57.7%)	18 (31.0%)	2 (3.38%)	5 (8.47%)
Age *N* (% C-AL lineage-age group ; % of all C-AL; % in age group; % of A-AL)					
Birth to <1 month	37 (11.7%)	24 (70.6%; 40.6%; 63.1%; 7.38%)	8 (44.4%; 13.6%; 21.1%; 2.46%)	2 (100%; 3.39%; 5.26%; 0.61%)	4 (80.0%; 6.77%; 10.5%; 1.23%)
≥1 to < 2 months	23 (6.4%)	10 (29.4%; 16.9%; 47.6%; 3.07%)	10 (55.6%; 16.9% 47.6%; 3.07%)	**	1 (20.0%; 1.69%; 4.76%; 0.31%)

Note. Chi square (α = .05). Age at birth vs. C-AL type $X^2 = 4.676$, $p = .197$. AL = acute leukemia. C-AML = congenital acute myeloid leukemia (birth to < 2 months). C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). C-OAL = congenital other acute leukemia (birth to < 2 months). **Null cases reported.

Research Question 2.2. "What is the proportion of infant AML and ALL in 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12-month-old infants?" To address Research Question 2.2 the infants diagnosed with acute leukemia were divided into AML, ALL, ALAL, or OAL, given not all infant acute leukemia retrieved from the SEER registry are consistent with the two distinct lineages myeloid (AML), lymphoid (ALL), but also acute leukemia of ambiguous lineage and an "other" category for uncategorized other acute leukemia. The AML, ALL, ALAL, and OAL groups were subsequently divided by estimated age at diagnosis 2 months or more to less than 12 months infant groups (I-AML, I-ALL, I-ALAL, and I-OAL). The I-AML, I-ALL, I-ALAL, and I-OAL groups were divided into estimated age at diagnosis from 2 months or more to less than 3 (I-AML$^{2-3}$, I-ALL$^{2-3}$, I-ALAL$^{2-3}$, and I-OAL$^{2-3}$), 3 months or more to less than 4 months (I-AML$^{3-4}$, C-ALL$^{3-4}$, I-ALAL$^{3-4}$, and I-OAL$^{3-4}$), 4 months or more to less than 5 months (I-AML$^{4-5}$, I-ALL$^{4-5}$, I-ALAL$^{4-5}$, and I-OAL$^{4-5}$), 5 months or more to less than 6 months (I-AML$^{5-6}$, I-ALL$^{5-6}$, I-ALAL$^{5-6}$, and I-OAL$^{5-6}$), 6 months or more to less than 7 months (I-AML$^{6-7}$, I-ALL$^{6-7}$, I-ALAL$^{6-7}$, and I-OAL$^{6-7}$), 7 months or more to less than 8 months (I-AML$^{7-8}$, I-ALL$^{7-8}$, I-ALAL$^{7-8}$, and I-OAL$^{7-8}$), 8 months or more to less than 9 months (I-AML$^{8-9}$, I-ALL$^{8-9}$, I-ALAL$^{8-9}$, and I-OAL$^{8-9}$), 9 months or more to less than 10 months (I-AML$^{9-10}$, I-ALL$^{9-10}$, I-ALAL$^{9-10}$, and I-OAL$^{9-10}$), 10 months or more to less than 11 months (I-AML$^{10-11}$, I-ALL$^{10-11}$, I-ALAL$^{10-11}$, and I-OAL$^{10-11}$), and 11months or more to less than 12 months (I-AML$^{11-12}$, I-ALL$^{11-12}$, I-ALAL$^{11-12}$, and I-OAL$^{11-12}$). The diagnoses included I-AML (113, 34.8% of I-AL), I-ALL (141, 43.4% of I-AL), I-ALAL (10, 3.08% of I-AL), and I-OAL (2, 0.62% of I-AL). The question was addressed using descriptive statistics of age groups (see Table 35). The chi-square test was used to evaluate the association between the age at diagnoses and I-AL type. An evaluation of age at diagnoses and I-AL type was made using the chi-square test =$X^2 = 26.28$, $p = .503$. The null hypothesis of the

test is that the age of diagnosis would not be significantly related to proportion of leukemia diagnosed by each lineage type. There was no statistically significant relationship between age at diagnoses and I-AL type, meaning I-AML, I-ALL, I-ALAL, and I-OAL are equally likely to be diagnosed in all I-AL^{B-12} groups. The largest number of leukemia diagnoses occurred from 11 to under 12 months of age (41, 12.6% of A-AL), and the lowest number of diagnoses was in the children aged 3 to 4 months (16, 4.9% of A-AL).

Table 35
The Leukemia Lineage of 266 Infants with Leukemia by Age of Diagnosis from the SEER Database, 2008-2014 for Leukemia Lineage Age Groups

	(AL %)	I-AML (% of I-AL)	I-ALL (% of I-AL)	I-ALAL (% of I-AL)	I-OAL (% of I-AL)
N (% I-AL lineage-age group; % of all I-AL; % in age group; % of A-AL)	266 (81.8%)	113 (34.8%)	141 (43.4%)	10 (3.08%)	2 (0.62%)
Age					
≥2 to < 3 months	18 (5.54%)	4 (3.54%; 1.50%; 0.22% 1.23%)	13 (9.22%; 4.88%; 72.2%; 4.00%)	**	1 (50.0%; 0.31%; 5.56%; 0.30%)
≥ 3 to < 4 months	16 (4.9%)	4 (3.54%; 1.50%; 25.0%; 1.23%)	11 (7.80%; 4.14%; 68.8%; 3.38%)	1 (100.0%; 0.31%; 6.25%; 0.30%)	**
≥ 4 to < 5 months	25 (7.69%)	12 (10.6%; 4.51%; 48.0%; 3.69%)	10 (7.09%; 3.76%; 40.0%; 3.07%)	2 (20.0%; 0.75%; 8.00%; 0.62%)	1 (50.0%; 0.31%; 4.00%; 0.30%)
≥ 5 to < 6 months	25 (7.69%)	11 (9.73%; 4.14%; 44.0%; 3.38%)	12 (8.51%; 4.51%; 48.0%; 3.69%)	2 (20.0%; 0.75%; 8.00%; 0.62%)	**

(continued)

Age		I-AML (% of I-AL)	I-ALL (% of I-AL)	I-ALAL (% of I-AL)	I-OAL (% of I-AL)
≥ 6 to < 7 months	24 (7.38%)	10 (8.8%; 3.76%; 41.7%; 3.07%)	14 (9.92%; 5.26%; 58.3%; 4.30%)	**	**
≥ 7 to < 8 months	34 (10.5%)	12 (10.6%; 4.51%; 35.3%; 3.69%)	20 (14.1%; 7.52%; 58.8%; 6.15%)	2 (20.0%; 0.75%; 5.88%; 0.62%)	**
≥ 8 to < 9 months	27 (8.31%)	15 (13.3%; 5.63%; 55.6%; 4.62%)	12 (8.51%; 4.51%; 44.4% 3.69%)	**	**
≥ 9 to < 10 months	28 (8.62%)	14 (12.4%; 5.26%; 50.0%; 4.30%)	14 (9.92%; 5.26%; 50.0%; 4.30%)	**	**
≥ 10 to < 11 months	28 (8.62%)	10 (8.85%; 3.76%; 35.7% 3.07%)	17 (12.1%; 6.39%; 60.7%; 5.23%)	1 (10.0%; 0.31%; 3.58% 0.30%)	**
≥ 11 to < 12 months	41 (12.6%)	21 (18.6%; 7.89%; 51.2% 6.46%)	18 (12.8%; 6.76%; 42.9%; 5.54%)	2 (20.0%; 0.75%; 4.88% 0.62%)	**

Note. AL% $N = 325$. Chi square ($\alpha = .05$). Age at birth vs. I-AL type = $X^2 = 26.28$, $p = .503$. AL = acute leukemia. I-AL = all infant acute leukemia diagnoses. I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months), I-ALAL = infant ambiguous lineage acute leukemia (≥2 months to < 12 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). Standard **Null cases reported.

Research Question 2.3. "What is the proportion by sex of congenital AML, congenital ALL, infant AML, and infant ALL?" To address Research Question 2.3, the infants diagnosed with acute leukemia were divided into AML, ALL, ALAL, or OAL, given not all infant acute leukemia retrieved from the SEER registry are consistent with the two distinct lineages myeloid

(AML) and lymphoid (ALL) but also acute leukemia of ambiguous lineage and an "other" category for uncategorized other acute leukemia. The AML, ALL, ALAL, and OAL groups were subsequently divided by age at diagnosis: congenital (C, birth to < 2 months) or infant leukemia (≥ 2 to < 12 months). The C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL groups were divided by sex: male and female. The diagnoses included C-AML (male, 17, 5.23% of A-AL; female, 17, 5.23% of A-AL), C-ALL (male, 6, 1.85% of A-AL; female, 12, 3.69% of A-AL), C-ALAL (male, 1, 0.30% of A-AL; female, 1, 0.30% of I-AL), C-OAL (male, 2, 0.62% of I-AL; female, 3, 0.92% of I-AL), I-AML (male, 61, 18.8% of I-AL; female, 52, 16.0% of I-AL), I-ALL (male, 86, 26.5% of I-AL; female, 55, 16.9% of I-AL), I-ALAL (male, 6, 1.85% of I-AL; female, 4, 1.23% of I-AL), and I-OAL (male, 1, 0.30% of I-AL; female, 1, 0.30% of I-AL). The question was addressed using descriptive statistics of leukemia groups stratified by sex (see Table 36). The chi-square test was used to evaluate the association between the sex and I-AL type. An evaluation of sex of record and I-AL type was made using the chi-square test =$X^2 = 5.17$, $p = .639$. The null hypothesis of the test is that sex of record would not be significantly related to leukemia group diagnosed. There was no statistically significant relationship between sex of record and I-AL type, meaning C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL are equally likely to be diagnosed in female and male infants.

Table 36
The Sex of 325 Infants with Leukemia by Lineage from the SEER Database, 2008-2014 for Leukemia Lineage Age Groups

	C-AML	C-ALL	C-ALAL	C-OAL	I-AML	I-ALL	I-ALAL	I-OAL
Lineage age group totals, *N*	34	18	2	5	113	141	10	2
Male *N* = 180 *N* (% of lineage age group; % of sex in A-AL; % A-AL)	17 (50.0%; 9.44%; 5.23%)	6 (33.3% 3.33%; 1.85%)	1 (50.0%; 0.55%; 0.30%)	2 (40.0%; 1.11%; 0.62%)	61 (54.0%; 33.9%; 18.8%)	86 (61.0%; 47.7%; 26.5%)	6 60.0%; 3.3%; 1.85%)	1 (50.0%; 0.55%; 0.30%)
Female *N* = 145 *N* (% of lineage age group; % of sex in A-AL; % A-AL)	17 (50.0%; 11.7%; 5.23%)	12 (66.7%; 8.28%; 3.69%)	1 (50.0%; 0.69%; 0.30%)	3 (60.0%; 2.07%; 0.92%)	52 (46.0% 35.9%; 16.0%)	55 (39.0%; 37.9%; 16.9%)	4 (40.0%; 2.76%; 1.23%)	1 (50.0%; 0.69%; 0.30%)

Note. Chi square (α =.05). Sex vs. AL type = $X^2 = 5.17$, $p = .639$. AL = acute leukemia. C-AML = congenital acute myeloid leukemia (birth to < 2 months). C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). C-OAL = congenital other acute leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months).

Research Question 2.4. "What is the proportion by SEER registry region of congenital AML, congenital ALL, infant AML, and infant ALL?" To address Research Question 2.4, the infants diagnosed with acute leukemia were divided into AML, ALL, ALAL, or OAL, given not

all infant acute leukemia retrieved from the SEER registry are consistent with the two distinct lineages myeloid (AML) and lymphoid (ALL) but also acute leukemia of ambiguous lineage and an "other" category for uncategorized other acute leukemia. The AML, ALL, ALAL, and OAL groups were subsequently divided by age at diagnosis: congenital (birth to < 2 months) or infant leukemia (≥ 2 to < 12 months). The C-AML, C-ALL, C-ALAL, and C-OAL, groups were divided by SEER registry region. The question was addressed using descriptive statistics of leukemia groups stratified by SEER registry (see Table 37, Figure 26). The diagnoses included C-AML (11 registry areas), C-ALL (9 registry areas), C-ALAL (2 registry areas), C-OAL (4 registry areas), I-AML (17 registry areas), I-ALL (17 registry areas), I-ALAL (7 registry areas), and I-OAL (2 registry areas).

The C-AML diagnoses were reported in California (excluding San Francisco/San Jose-Monterey/Los Angeles [SF/SJM/LA], [10]), Connecticut (1), Detroit (Metropolitan [3]), Greater Georgia (1), Hawaii (4), Los Angeles (3), Louisiana (2), New Jersey (6), New Mexico (1), San Francisco-Oakland (San Francisco-Oakland Standard Metropolitan Statistical Area [SMSA], [2]), and Utah (1). The C-ALL diagnoses were reported in Atlanta (Metropolitan [1]), California (excluding SF/SJM/LA [6]), Connecticut (1), Detroit (Metropolitan [1]), Greater Georgia (1), Los Angeles (3), New Jersey (1), San Francisco-Oakland SMSA (1), and San Jose-Monterey (3). The C-ALAL diagnoses were reported in California (excluding SF/SJM/LA [1]) and Kentucky (1). The C-OAL diagnoses were reported in Atlanta (Metropolitan [1]), California (excluding SF/SJM/LA [2]), New Jersey (1), and Utah (1).

The I-AML diagnoses were reported in: Alaska Natives (1), Atlanta (Metropolitan [4]), California (excluding SF/SJM/LA [25]), Connecticut (4), Detroit (Metropolitan [6]), Greater Georgia (6), Hawaii (3), Iowa (3), Kentucky (3), Los Angeles (16), Louisiana (8), New Jersey

(4), New Mexico (3), San Francisco-Oakland SMSA (9), San Jose-Monterey (5), Seattle (Puget Sound [6]), and Utah (7). The I-ALL diagnoses were reported in Alaska Natives (1), Atlanta (Metropolitan [5]), California (excluding SF/SJM/LA [39]), Connecticut (1), Detroit (Metropolitan [6]), Greater Georgia (13), Hawaii (1), Iowa (2), Kentucky (9), Los Angeles (20), Louisiana (3), New Jersey (9), New Mexico (4), San Francisco-Oakland SMSA (3), San Jose-Monterey (8), Seattle (Puget Sound [8]), and Utah (9). The I-ALAL diagnoses were reported in California (excluding SF/SJM/LA [1]), Greater Georgia (2), Hawaii (1), Los Angeles (1), New Jersey (1), San Francisco-Oakland SMSA (2), and Utah (2). The I-OAL diagnoses were reported in California (excluding SF/SJM/LA [1]), and Los Angeles (1).

Research Question 2.4.1. "What are the characteristics of the highest proportion SEER registry region counties (where diagnosed) by families below poverty, person below 100%, number unemployed in county, median family income, and number of foreign born individuals?" To address Research Question 2.4.1, the infant cases diagnosed with acute leukemia were divided by SEER registry area. The question was evaluated with descriptive statistics, including a table comparison of the reported cases within the top 20% of all registry areas (see Table 39). The registry areas with the top 20% of all cases included California (excluding SF/SJM/LA; 85, 26.2% of I-AL), Greater Georgia (23, 7.1% of I-AL), Los Angeles (44, 13.5% of I-AL), and New Jersey (23, 7.1% of I-AL).

Table 37

The Distribution of Congenital versus Infant Acute Leukemia in 325 Infants by SEER Registry Region Stratified Groups from the SEER Database, 2008-2014 for Leukemia Lineage Age Groups

	N (A-AL %)	C-AML (% of I-AL)	C-ALL, *N* (% of I-AL)	C-ALAL*N* (% of I-AL)	C-OAL, *N* (% of I-AL)	I-AML, *N* (% of I-AL)	I-ALL, *N* (% of I-AL)	I-ALAL, *N* (% of I-AL)	I-OAL, *N* (% of I-AL)
Lineage age group totals		34 (10.5 %)	18 (5.5%)	2 (0.6%)	5 (1.5%)	113 (34.8%)	141 (43.4%)	10 (3.1%)	2 (0.6%)
SEER Registry									
Alaska Natives	2 (0.62 %)	**	**	**	**	1 (0.30%)	1 (0.30%)	**	**
Atlanta (Metropolitan)	11 (3.4%)	**	1 (0.30%)	**	1 (0.30 %)	4 (1.23%)	5 (1.53%)	**	**
California (excluding SF/SJM/ LA)†	85 (26.2 %)	10 (3.07 %)	6 (1.85%)	1 (0.30%)	2 (0.62 %)	25 (7.69%)	39 (12.0%)	1 (0.30%)	1 (0.30%)
Connecticut	7 (2.2%)	1 (0.30 %)	1 (0.30%)	**	**	4 (1.23%)	1 (0.30%)	**	**
Detroit (Metropolitan)	17 (5.23 %)	3 (0.92 %)	1 (0.30%)	**	**	6 (1.85%)	6 (1.85%)	**	**
Greater Georgia	23 (7.1%)	1 (0.30 %)	1 (0.30%)	**	**	6 (1.85%)	13 (4.0%)	2 (0.62%)	**
Hawaii	9 (2.8%)	4 (1.23 %)	**	**	**	3 (0.92%)	1 (0.30%)	1 (0.30%)	**
Iowa	5 (1.5%)	**	**	**	**	3 (0.92%)	2 (0.62%)	**	**
Kentucky	13 (4.0%)	**	**	1 (0.30%)	**	3 (0.92%)	9 (2.77%)	**	**

(continued)

	N (A-AL %)	C-AML (% of I-AL)	C-ALL, *N* (% of I-AL)	C-ALAL*N* (% of I-AL)	C-OAL, *N* (% of I-AL)	I-AML, *N* (% of I-AL)	I-ALL, *N* (% of I-AL)	I-ALAL, *N* (% of I-AL)	I-OAL, *N* (% of I-AL)
Los Angeles	44 (13.5 %)	3 (0.92 %)	3 (0.92%)	**	**	16 (4.92%)	20 (6.15%)	1 (0.30%)	1 (0.30%)
Louisiana	13 (4.0%)	2 (0.62 %)	**	**	**	8 (2.46%)	3 (0.62%)	**	**
New Jersey	22 (6.8%)	6 (1.85 %)	1 (0.30%)	**	1 (0.30 %)	4 (1.23%)	9 (2.77%)	1 (0.30%)	**
New Mexico	8 (2.5%)	1 (0.30 %)	**	**	**	3 (0.92%)	4 (1.23%)	**	**
San Francisco-Oakland SMSA‡	17 (5.23 %)	2 (0.62 %)	1 (0.30%)	**	**	9 (2.77%)	3 (0.92%)	2 (0.62%)	**
San Jose-Monterey	16 (4.9%)	**	3 (0.92%)	**	**	5 (1.53%)	8 (2.46%)	**	**
Seattle (Puget Sound)	14 (4.3%)	**	**	**	**	6 (1.85%)	8 (2.46%)	**	**
Utah	20 (6.2%)	1 (0.30 %)	**	**	1 (0.30 %)	7 (2.15%)	9 (2.77%)	2 (0.62%)	**

Note. A-AL% N = 325. I-AL = all acute leukemia in infants <12 months. C-AML = congenital acute myeloid leukemia (birth to < 2 months). C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). C-OAL = congenital other acute leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). †California (excluding SF/SJM/LA). ‡San Francisco-Oakland Standard Metropolitan Statistical Area. **Null cases reported.

These registry areas were further evaluated by socio-economic characteristics of families below poverty, person below 100% of poverty, number unemployed in county, median family income, and number of foreign born individuals (see Table 38). The families below poverty (100%) characteristic evaluated for mean, median, and plus or minus *SD* included California

(excluding SF/SJM/LA; 11.9%, 12.16%, ± 4.7), Greater Georgia (13.9%, 13.9% ± 5.3), Los Angeles (13.6%, 13.6%; with data collected from one county), and New Jersey (7.1%, 5.4% ± 3.8). The persons below poverty (100%) characteristic was evaluated for mean, median, and plus or minus *SD* and included California (excluding SF/SJM/LA; 16.03%, 16.03% ± 5.0), Greater Georgia (18.54%, 18.82% ± 7.8), Los Angeles (17.12%, 17.12%; with data collected from one county), and New Jersey (9.37%, 8.01% ± 4.25)

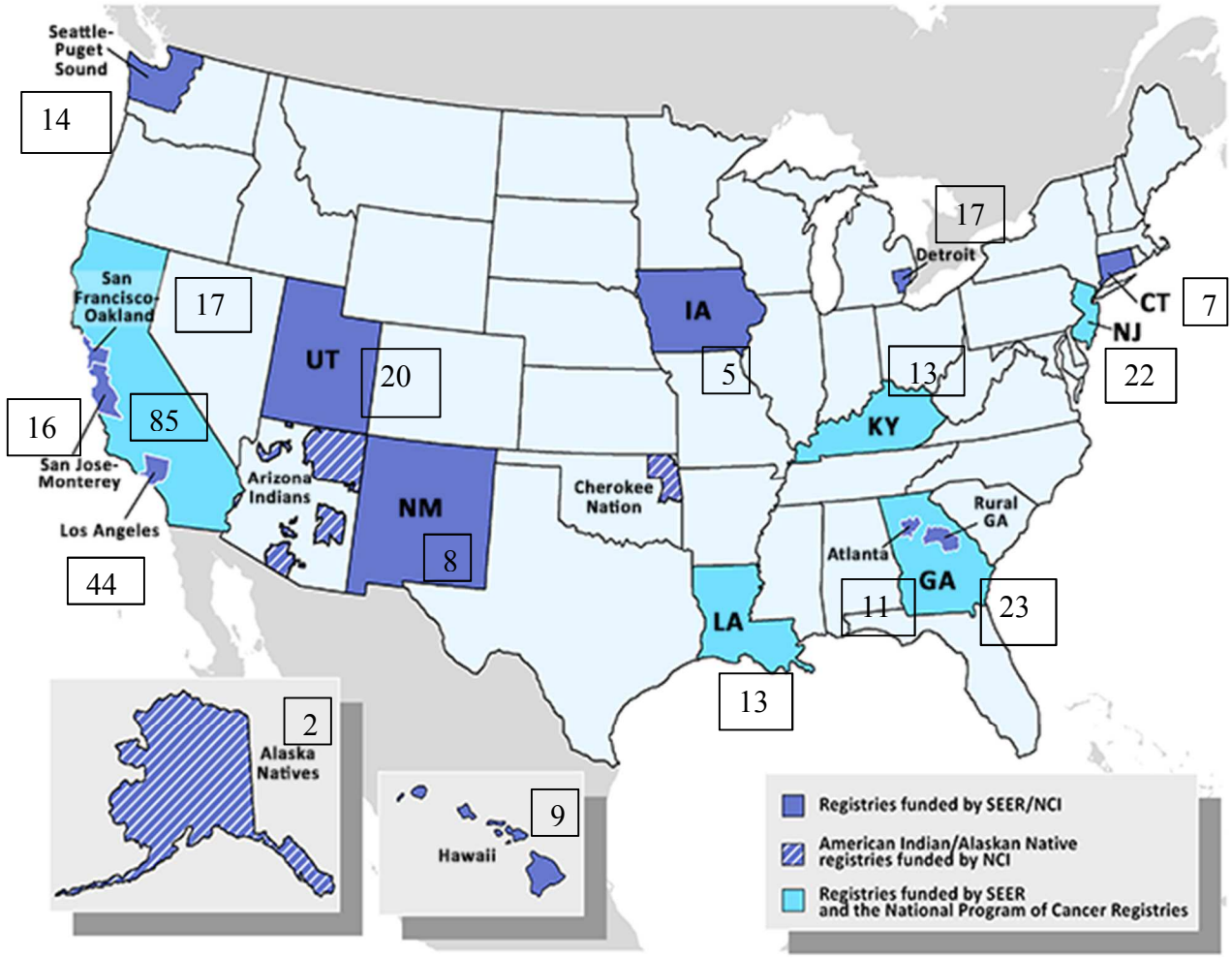


Figure 26: SEER registry areas. Geographical representation SEER registry area of 325 infants with congenital/infant leukemia diagnosed ≤ 12 months of age from the SEER database, 2008–2014. Adapted from "About the SEER Registries," by National Cancer Institute, 2019, (https://seer.cancer.gov/registries/). Copyright 2019 by National Cancer Institute.

The "% unemployed" characteristic was evaluated for mean, median, and plus or minus *SD* and included California (excluding SF/SJM/LA; 12.0%, 12.3%, ± 2.51), Greater Georgia (9.7%, 9.5% ±2.3), Los Angeles (10.8, 10.8; with data collected from one county), and New Jersey (9.37%, 8.01% ± 4.25). The median family income ($/year) characteristic was evaluated for mean plus or minus *SD* and included California (excluding SF/SJM/LA; $66,820 ± 13,537), Greater Georgia ($57,556 ± 14,779), Los Angeles ($62,630; with data collected from one county), and New Jersey ($90,587 ± 17,986). The number of foreign born individuals (*N* ± *SD*) characteristic was evaluated for mean and plus or minus SD and included California (excluding SF/SJM/LA; 19,690 ± 5,575), Greater Georgia (5,813 ± 4,068), Los Angeles (3,530; with data collected from one county), and New Jersey (22,123 ± 10,646).

Table 38
The Socio-Economic Characteristics of the Highest Proportion SEER Registry Area Counties (Top 20% of Cases) from the SEER Database, 2008-2014

	N (% of A-AL)	Families below poverty (100%), mean, median, ±SD	Persons below poverty (100%) mean, median, ± SD	% unempl-oyed mean, median, ± SD	median family income mean *$/year* ± SD	number of foreign born individuals *N* ± SD
California (excluding SF/SJM/LA) †	85 (26.2%)	11.9%, 12.16%, ±4.7	16.03%, 16.03% ±5.0	12.0%, 12.3%, ±2.51	$66,820 ±13,537	19,690 ±5,575
Greater Georgia	23 (7.1%)	13.9%, 13.9% ±5.3	18.54%, 18.82% ±7.8	9.7%, 9.5% ±2.3	$57,556 ±14,779	5,813 ± 4,068
Los Angeles*	44 (13.5%)	13.6%, 13.6%	17.12%, 17.12%	10.8, 10.8	$62,630	3,530
New Jersey	22 (6.8%)	7.1%, 5.4% ±3.8	9.37%, 8.01%, ±4.25	9.3, 9.9 ±1.7	$90,587 ±17,986	22,123 ±10,646

Note. N = 175. % of A-AL = 53.8%. †California (excluding SF/SJM/LA). *LA data reported from a single county.

Research Question 2.5. "What is the cause of death proportion by congenital AML, congenital ALL, infant AML, and infant ALL?" To address Research Question 2.5, the infants diagnosed with acute leukemia were divided into AML, ALL, ALAL, or OAL, given not all infant acute leukemia retrieved from the SEER registry are consistent with the two distinct lineages myeloid (AML) and lymphoid (ALL) but also acute leukemia of ambiguous lineage and an "other" category for uncategorized other acute leukemia. The AML, ALL, ALAL, and OAL groups were subsequently divided by age at diagnosis: congenital (birth to < 2 months) or infant leukemia (≥ 2 to < 12 months). The C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL groups were subsequently divided by vital status: alive or dead (death attributable to this cancer diagnosis).

The C-AML, C-ALL, C-ALAL, and C-OAL, groups were first divided by vital status. The question was addressed using descriptive statistics of leukemia groups stratified by vital status (see Table 39). The diagnoses included C-AML (28 alive, 6 dead, attributable to this cancer diagnosis), C-ALL (10 alive, 8 dead, attributable to this cancer diagnosis), C-ALAL (1 alive), C-OAL (1 alive, 3 dead, attributable to this cancer diagnosis), I-AML (75 alive, 36 dead, attributable to this cancer diagnosis), I-ALL (97 alive, 36 dead, attributable to this cancer diagnosis), I-ALAL (5 alive, 5 dead, attributable to this cancer diagnosis), and I-OAL (1 alive, 1 dead, attributable to this cancer diagnosis) with 12 infants without vital status reported to the SEER registry. The question was addressed using descriptive statistics of lineage age groups stratified by vital status. The chi-square test was used to evaluate the association between the vital status and lineage-age group. An evaluation of vital and I-AL type was made using the chi-square test =$X^2 = 9.91$, $p = .194$. The null hypothesis of the test was that vital status (alive or dead) would not be significantly related to leukemia group diagnosed. There was no statistically

significant relationship between vital status (alive or dead) and lineage age group, meaning C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL are equally likely to be alive or dead following treatment.

Table 39
The Vital Status of 325 Infants with Acute Leukemia from the SEER Database, 2008-2014

	Vital Status		
	(% A-AL)	Alive *N* (% of lineage-age group)	Dead‡ *N* (% of lineage-age group)
C-AML	34 (10.5%)	28 (82.4%)	6 (17.6%)
C-ALL	18 (5.54%)	10 (55.6%)	8 (44.4%)
C-ALAL	2 (0.62%†)	1 (50.0%)	**
C-OAL	5 (1.54%†)	1 (20.0%)	3 (60.0%)
I-AML	113 (34.8%†)	75 (66.4%)	36 (31.9%)
I-ALL	141 (43.4%†)	97 (68.8%)	36 (25.5%)
I-ALAL	10 (0.30%)	5 (50.0%)	5 (50.0%)
I-OAL	2 (0.62%)	1 (50.0%)	1 (50.0%)

Note. $N = 325$. Chi square ($\alpha = .05$). Death vs. lineage-age group = $X^2 = 9.91$, $p = .194$. C-AML = congenital acute myeloid leukemia (birth to < 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months), C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). ‡Death attributable to this cancer diagnosis. † The values within table are not a sum given alive/death status available for 321 infants only from the SEER registry. **Null cases reported.

To further address research question 2.6, the C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL, groups were divided and evaluated by cause of death. The question was addressed using descriptive statistics of leukemia groups stratified by COD categories: COD site recode, cause specific death classification, and other cause of death

classification (see Table 40, Table 41, Table 42, Table 43, Table 44, Table 45, Table 46, and Table 47).

The C-AML COD included (6 dead attributable to this cancer diagnosis): (a) certain conditions originating in the perinatal period (1, 2.9%), (b) congenital anomalies include inherited disorders and/or disorders arising before birth (3, 8.8%), and (c) no known status/other (state not available or state DC available but no COD; 2, 5.9%; see Table 40). The C-ALL COD included (8 dead attributable to this cancer diagnosis): with no further COD information (see Table 41). The C-ALAL COD included (1 without posttreatment status reported): no known status/other (state not available or state DC available but no COD; 1, 50.0%; see Table 42). The C-OAL COD included (3 dead attributable to this cancer diagnosis, 4 dead): certain conditions originating in the perinatal period (1, 20.0%) and in situ, benign, or unknown behavior neoplasm (1, 20.0%; see Table 43).

The I-AML COD included (36 dead attributable to this cancer diagnosis): (a) infectious and parasitic diseases, including HIV (1, 0.90%); (b) brain and other nervous system diseases (1, 0.90%); and (c) n/a not first tumor (2, 1.8%; see Table 44). The I-ALL COD included (36 dead attributable to this cancer diagnosis): (a) n/a not first tumor (1, 0.7%); (b) other cause of death (4, 2.8%); (c) infectious and parasitic diseases, including HIV (1, 0.7%); (d) pneumonia and influenza (1, 0.7%); and (e) no known status/other (state not available or state DC available but no COD; 1, 0.7%; see Table 45). The I-ALAL COD included (5 dead attributable to this cancer diagnosis) with no further COD information (see Table 46). The I-OAL COD included (1 dead attributable to this cancer diagnosis) with no further COD information (see Table 47).

Table 40
The Cause of Death of 34 Infants with Congenital Acute Myeloid Leukemia from the SEER Database, 2008-2014

	Vital Status			Cause of Death		
	N (total)	Alive *N* (% C-AML)	Dead† *N* (% C-AML)	Conditions of perinatal period *N* (% C-AML)§	Congenital anomalies‡ *N* (% C-AML)	No known status/ other* *N* (% C-AML)
C-AML	34	28 (82.4%)	6 (17.7%)	1 (2.9%)	3 (8.8%)	2 (5.9%)

Note. C-AML = congenital acute myeloid leukemia (birth to < 2 months). †Death attributable to this cancer diagnosis; §Certain conditions originating in the perinatal period. *State not available or state DC available but no COD.

Table 41
The Cause of Death of 18 Infants with Congenital Acute Lymphoblastic Leukemia from the SEER Database, 2008-2014

	Vital Status			Cause of Death	
	N (total)	Alive *N* (% C-ALL*)*	Dead† *N* (% C-ALL)	Other causes (COD)§ *N* (% C-ALL)	No known status other* *N* (% C-ALL)
C-ALL	18	(10, (55.6%)	(8, 44.4%)	**	**

Note. C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). **Null cases reported; †Death attributable to this cancer diagnosis. §No categorization. *State not available or state DC available but no COD.

Table 42
The Cause of Death of Two Infants with Congenital Ambiguous Acute Leukemia from the SEER Database, 2008-2014

	Vital Status			Cause of Death
	N (total)	Alive *N* (% C-ALAL)	Dead† *N* (% C-ALAL)	No known status/other* *N* (% total)
C-ALAL	2	1 (50.0%)	**	1 (50.0%)

Note. C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). †Death attributable to this cancer diagnosis. *State not available or state DC available but no COD.

Table 43
The Cause of Death of Five Infants with Congenital Other Acute Leukemia from the SEER Database, 2008-2014

	Vital Status			Cause of Death	
	N (total)	Alive *N* (% C-AOL)	Dead† *N* (% C-AOL)	Conditions of perinatal period§ *N* (% C-AOL)	In situ, benign or unknown behavior neoplasm *N* (% C-AOL)
C-OAL	5	1 (20.0%)	3 (60.0%)	1 (20.0%)	1 (20.0%)

Note. C-OAL = congenital other acute leukemia (birth to < 2 months). †Death attributable to this cancer diagnosis. §Certain conditions originating in the perinatal period.

Table 44
The Cause of Death of 113 Infants with Infant Acute Myeloid Leukemia from the SEER Database, 2008-2014

	Vital Status			Cause of Death		
	N (total)	Alive *N* (% I-AML)	Dead† *N* (% I-AML)	Infectious and parasitic diseases§ *N* (% I-AML)	Nervous system *N* (% I-AML)	N/A not first tumor *N* (% I-AML)
I-AML	113	75 (66.4%)	36 (31.9%)	1 (0.88%)	1 (0.88%)	2 (1.8%)

Note. I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months); †Death attributable to this cancer diagnosis; §Infectious and parasitic diseases including HIV.

Table 45
The Cause of Death of 141 Infants with Infant Acute Lymphoblastic Leukemia from the SEER Database, 2008-2014

	Vital Status			Cause of Death				
	N (total)	Alive *N* (% I-ALL)	Dead† *N* (% I-ALL)	N/A not first tumor∂ *N* (% I-ALL)	Other cause of death¦ *N* (% I-ALL)	Infectious and parasitic disease§ *N* (% I-ALL)	Pneumonia and influenza *N* (% I-ALL)	No known status/ other* *N* (% I-ALL)
I-ALL	141	97 (68.8%)	36 (25.5%)	1 (0.7%)	4 (2.8%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

Note. I-ALL = infant acute lymphoblastic leukemia (≥ 2 months to < 12 months). †Death attributable to this cancer diagnosis. ∂Cause of death not attributable to the current cancer diagnosis. ¦No categorization. §Infectious and parasitic diseases, including HIV. *State not available or state DC available but no COD.

Table 46
The Cause of Death of 10 Infants with Infant Ambiguous Lineage Acute Leukemia from the SEER Database, 2008-2014

		Vital Status	
	N (total)	Alive *N* (%I-ALAL)	Dead† *N* (% I-ALAL)
I-ALAL	10	5 (50.0%)	5 (50.0%)

Note. I-ALL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). †Death attributable to this cancer diagnosis.

Table 47
The Cause of Death of Two Infants with Infant Other Acute Leukemia from the SEER Database, 2008-2014

		Vital Status	
	N (total)	*Alive* *N* (% I-OAL)	*Dead*† *N* (% I-OAL)
I-OAL	2	1 (50.0%)	1 (50.0%)

Note. I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). †Death attributable to this cancer diagnosis.

Research Question 3. "How do the characteristics of AML and ALL differ, addressing differences in mortality over time between 2008-2014 in the United States?" To first address this question, the cause of death after acute leukemia diagnosis (109) was designated as cancer or non-cancer related (see Figure 27).

To specifically address Research Question 3, the infants diagnosed with acute leukemia were divided by year of diagnosis: 2008, 2009, 2010, 2011, 2012, 2013, and 2014. After the

groups were first divided by year of diagnosis status, the question was addressed using descriptive statistics of leukemia groups stratified by posttreatment status (see Table 48). The diagnoses by year included 2008 (45, 13.8%), 2009 (42, 12.9%), 2010 (53, 16.3%), 2011

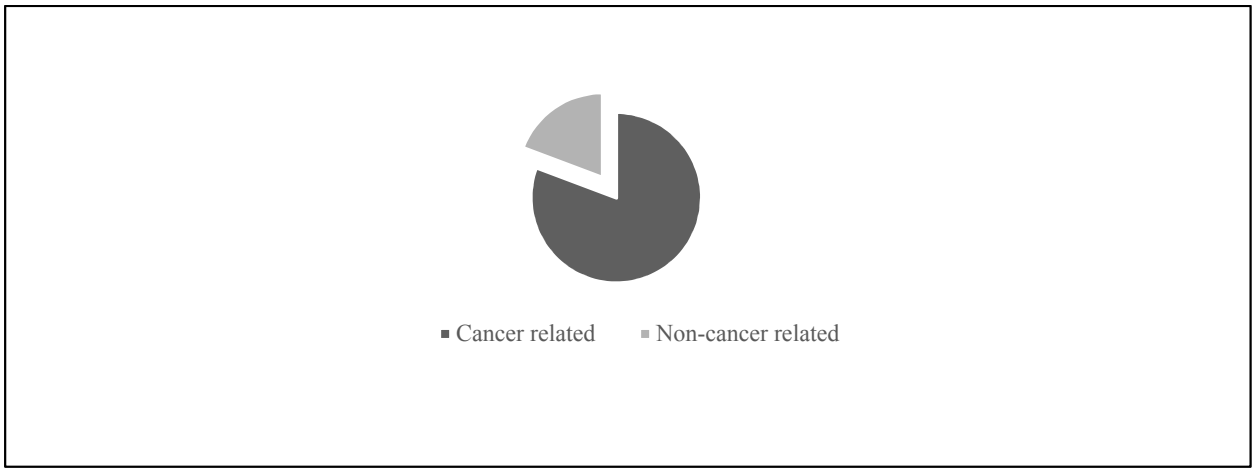


Figure 27. Cause of death after acute leukemia diagnosis for 109 infants in the case series. Cause of death separated by cancer or non-cancer related death.

(44,13.5%), 2012 (47, 14.5%), 2013 (46, 14.2%), and 2014 (48, 14.8%). The diagnoses by year stratified by posttreatment status included 2008 (29 alive [64.4%]), 16 dead attributable to this cancer diagnosis (35.5%), 2009 (24 alive [57.1%]), 17 dead attributable to this cancer diagnosis (40.5%), 2010 (29 alive [54.7%]), 23 dead attributable to this cancer diagnosis (43.4%), one no known status/state not available or state DC available but no COD (2.39%), 2011 (30 alive, 14 dead attributable to this cancer diagnosis), 2012 (28 alive, 19 dead attributable to this cancer diagnosis), 2013 (33 alive, 12 dead attributable to this cancer diagnosis, 1 no known status/state not available or state DC available but no COD), and 2014 (39 alive, 8 dead attributable to this cancer diagnosis, 1 no known status/state not available or state DC available but no COD). The question was addressed further using descriptive statistics of year of diagnosis groups stratified by posttreatment status, including deaths reported and values calculated for each year. An evaluation of posttreatment status and the case series included (a) alive (212, $\bar{X}$ = 65.2%), (b)

dead (109, $\bar{X}$ = 33.5%), and (c) no known status/state not available or state DC available but no COD (4, $\bar{X}$ = 1.2%). The majority of infants diagnosed with acute leukemia in this case series were alive at most recent update to the SEER registry data (April 16, 2018) prior to access of case series record data for this dissertation study.

Table 48
The Posttreatment Status of 325 Infants with Acute Leukemia by Diagnosis Year from the SEER Database, 2008-2014

	Posttreatment Status			
	N (A-AL %)	Alive *N* (*% yDx*)	Dead *N* (% *yD*x)	No known status/other* *N* (% *yDx*)
Year of diagnosis				
2008	45 (13.8%)	29 (64.4%)	16 (35.5%)	**
2009	42 (12.9%)†	24 (57.1%)	17 (40.5%)	1 (2.39%)
2010	53 (16.3%)†	29 (54.7%)	23 (43.4%)	1 (1.59%)
2011	44 (13.5%)†	30 (68.2%)	14, (31.8%)	**
2012	47 (14.5%)†	28 (59.6%)	19 (40.4%)	**
2013	46 (14.2%)†	33 (71.7%)	12 (26.1%)	1 (2.17%)
2014	48 (14.8%)	39 (81.3%)	8 (16.7%)	1 (2.08%)
Mean *N* $\bar{X}$ %		212 $\bar{X}$ = 65.2%	109 $\bar{X}$ = 33.5%	4 $\bar{X}$ = 1.2%

Note. yDx = year of diagnosis. AL = acute leukemia (birth to < 12 months). *State not available or state DC available but no COD. ** Null cases reported

Research Question 3.1. "How do the mortality rates among congenital AML, congenital ALL, infant AML, and infant ALL differ during this period?" To address research question 3.1 the infants diagnosed with acute leukemia were divided by year of diagnosis: 2008, 2009, 2010, 2011, 2012, 2013, and 2014. After the groups were first divided by year of diagnosis status, the question was first addressed using descriptive statistics of leukemia group diagnosis year groups

stratified by posttreatment status (see Table 48). The findings included a range of diagnoses per year from 42 to 53 cases during 2008 to 2014 with the largest number of diagnoses (53) occurring in 2010 and the fewest (42) in 2009.

In 2008, the C-AML diagnoses (4) posttreatment statuses included (a) C-AML alive (C-AML^{A}[1]) and C-AML dead (C-AML^{D} [3]); (b) C-ALL diagnoses (3), C-ALL alive (C-ALL ^{A}[1]), and C-ALL^{D} dead (C-ALL^{D} [2]); (c) there were no C-ALAL diagnoses in 2008; (d) C-OAL diagnoses (1) and C-OAL alive (C-OALL^{A} [1]); I-AML diagnoses (17) alive, (I-AML^{A} [13]), and I-AML dead (I-AML^{D} [4]); (d) I-ALL diagnoses (20), I-ALL alive (I-ALL ^{A} [13), and I-ALL^{D} dead (I-ALL^{D} [7]); and (e) there were no I-ALAL or I-OAL diagnoses in 2008.

In 2009, the C-AML diagnoses (5) posttreatment statuses included (a) C-AML^{A} (3) and (C-AML^{D} [2]; (b) C-ALL diagnoses (3), C-ALL ^{A} (1), and C-ALL^{D} (2); (c) C-ALAL diagnoses (1) and state DC not available or state DC available but no COD; (d) there were no C-OAL diagnoses in 2009; (e) I-AML diagnoses (13), I-AML^{A} (7), and I-AML^{D} (6); I-ALL diagnoses (18), I-ALL ^{A} (11), and I-ALL^{D} (7); (f) I-ALAL diagnoses (2) and I-ALAL ^{A} (2); and (g) there were no I-OAL diagnoses in 2009.

In 2010, the C-AML diagnoses (4) posttreatment statuses included (a) C-AML^{A} (4); (b) the C-ALL diagnoses (1) and C-ALL^{D} (1); (c) there were no C-ALAL diagnoses in 2010; (d) C-OAL diagnoses (1) and C-OAL^{D} (1); (e) I-AML diagnoses (26), I-AML^{A} (14), and I-AML^{D} (12); (f) the I-ALL diagnoses (19), I-ALL ^{A} (10), I-ALL^{D} (8), and state DC not available or state DC available but no COD (1); (g) the I-ALAL (1) and I-ALAL ^{D} (1); and (h) there were no I-OAL diagnoses in 2010.

In 2011, the C-AML diagnoses (5) posttreatment statuses included (a) C-AML^{A} (3) and C-AML^{D} (2); (b) C-ALL diagnoses (2), C-ALL ^{A} (1), and C-ALL^{D} (1); (c) there were no C-

ALAL or C-OAL diagnoses in 2011; (d) I-AML diagnoses (10), I-AML^{A} (8), and I-AML^{D} (2); (e) the I-ALL diagnoses (23), I-ALL ^{A} (16), and I-ALL^{D} (7); (f) the I-ALAL (3), I-ALAL ^{A} (2), and (I-ALAL ^{D}[1]); and (g) the I-OAL diagnoses (1) and I-OAL (I-OAL^{D} [1]).

In 2012, the C-AML diagnoses (5) posttreatment statuses included (a) C-AML^{A} (3) and C-AML^{D} (2); (b) C-ALL diagnoses (4), C-ALL ^{A} (3), and C-ALL^{D} (1); (c) there were no C-ALAL diagnoses in 2011; (d) the C-OAL diagnoses (1) and C-OAL^{D} (1); (e) I-AML diagnoses (14), I-AML^{A} (6) and I-AML^{D} (8); (f) the I-ALL diagnoses (24), I-ALL ^{A} (16) and I-ALL^{D} (6); (g) the I-ALAL (2), I-ALAL ^{D} (1), and state DC not available or state DC available but no COD (1); and (h) there were no I-OAL diagnoses in 2012.

In 2013, the C-AML diagnoses (6) posttreatment statuses included (a) C-AML^{A} (5) and C-AML^{D} (1); (b) the C-ALL diagnoses (2), C-ALL ^{A} (1), and C-ALL^{D} (1); (c) the C-ALAL diagnoses (2) and I-ALAL^{D} (1); (d) the C-OAL diagnoses (2) and C-OAL^{D} (2); (e) I-AML diagnoses (11), I-AML^{A} (9), and I-AML^{D} (2); (f) the I-ALL diagnoses (19), I-ALL ^{A} (16), and I-ALL^{D} (3); (g) the I-ALAL (2), I-ALAL ^{D} (1), state DC not available or state DC available but no COD (1); and (h) the I-OAL diagnoses (1) and I-OAL^{A} (1).

In 2014, the C-AML diagnoses (3) posttreatment statuses included (a) C-AML^{A} (3); (b) the C-ALL diagnoses (3) and C-ALL ^{A} (3); (c) there were no C-ALAL or C-OAL diagnoses in 2014; (d) I-AML diagnoses (20), I-AML^{A} (17), and I-AML^{D} (3); (e) the I-ALL diagnoses (20), I-ALL ^{A} (15), and I-ALL^{D} (5); (f) the I-ALAL diagnoses (1) and I-ALAL ^{A} (1); and (g) there were no I-OAL diagnoses in 2014.

The percentage of infants who were designated alive as their posttreatment status from their AL diagnoses fluctuated from 55.8% to 81.3% between 2008 to 2014: 2008 (29, 64.4%), 2009 (24, 58.5%), 2010 (29, 55.8%), 2011 (30, 68.1%), 2012 (28, 59.6%), 2013 (33, 73.3%), and

2014 (39, 81.3%). The percentage of infants who died from their AL diagnoses fluctuated from 17.0% to 44.2% between 2008 to 2014: 2008 (16, 35.6%), 2009 (17, 41.4%), 2010 (23, 44.2%), 2011 (14, 31.8%), 2012 (19, 40.4%), 2013 (12, 26.7%), and 2014 (8, 16.7%).

In the year 2008, there were 45 diagnoses (13.8% of A-AL), and 35.6% had death outcomes, accounting for 14.7% of all deaths in the case series (N = 109). In 2009, there were 42 diagnoses (12.9% of A-AL), and 41.4% had death outcomes, accounting for 15.6% of all deaths in the case series. In the year 2010, there were 53 diagnoses (16.3% of A-AL), and 44.2% had death outcomes, accounting for 21.1% of all deaths in the case series. In 2011, there were 44 diagnoses (13.5% of A-AL), and 31.8% had death outcomes, accounting for 12.8% of all deaths in the case series. In 2012, there were 47 diagnoses (14.5% of A-AL), and 40.4% had death outcomes, accounting for 17.4% of all deaths in the case series. In 2013, there were 46 diagnoses (14.2% of A-AL), and 26.7% had death outcomes, accounting for 11.0% of all deaths in the case series. In 2014, there were 48 diagnoses (14.8% of A-AL) with the lowest percentage of deaths in a diagnosis year (8,16.7%), accounting for 7.34% of all deaths in the case series.

The chi-square test was used to evaluate the association between the year of diagnosis and lineage age group. An evaluation of year of diagnoses and lineage age group was made using the chi-square test =X^2 = 33.51, p = .822. The null hypothesis of the test was that year of diagnosis would not be significantly related to leukemia group diagnosed. There was no statistically significant relationship between year of diagnosis and lineage age group, meaning C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL are equally likely to be diagnosed from 2008 to 2014.

Table 49

The Posttreatment Status of 325 Infants with Acute Leukemia by Age-Stratified Groups from the SEER Database, 2008-2014

	Posttreatment status						
Year of Diagnosis	2008	2009	2010	2011	2012	2013	2014
N yDx (% of A-AL)	45 (13.8%)	42 (12.9%)†	53 (16.3%)†	44 (13.5%)	47 (14.5%)	46 (14.2%)†	48 (14.8%)
N alive yDx (% of A-AL)	29 (64.4%)	24 (58.5%)	29 (55.8%)	30 (68.1%)	28 (59.6%)	33 (73.3%)	39 (81.3%)
	2008	2009	2010	2011	2012	2013	2014
N dead† yDx (% of A-AL)	16 (35.6%)	17 (41.4%)	23 (44.2%)	14 (31.8%)	19 (40.4%)	12 (26.7%)	8 (16.7%)
Leukemia group							
N, C-AML[A]	1	3	4	3	3	5	3
N, C-AML[D]	3	2	**	2	2	1	**
N, C-ALL[A]	1	1	**	1	3	1	3
N, C-ALL[D]	2	2	1	1	1	1	**
N, C-ALAL[A]	**	**	**	**	**	**	**
N, C-ALAL[D]	**	**	**	**	**	1	**
N, C-OAL[A]	1	**	**	**	**	**	**
N, C-OAL[D]	**	**	1	**	1	2	**
N, I-AML[A]	13	7	14	8	6	9	17
N, I-AML[D]	4	6	12	2	8	2	3
N, I-ALL[A]	13	11	10	16	16	16	15
N, I-ALL[D]	7	7	8	7	6	3	5
N, I-ALAL[A]	**	2	**	2	**	**	1
N, I-ALAL[D]	**	**	1	1	1	1	**

(continued)

	Posttreatment Status						
N, I-OAL [A]	**	**	**	**	**	1	**
N, I-OAL[D]	**	**	**	1	**	**	**

Note. Chi square (α =.05). Diagnosis year vs. lineage-age group = $X^2 = 33.5$, $p = .822$. yDx = year of diagnosis. C-AML = congenital acute myeloid leukemia (birth to ≥ 2 months). I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months); C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). I-ALL = infant acute lymphoid leukemia (≥ 2 months to < 12 months). C-ALAL = congenital ambiguous lineage acute leukemia (birth to < 2 months). I-ALAL = infant ambiguous lineage acute leukemia (≥ 2 months to < 12 months). C-OAL = congenital other acute leukemia (birth to < 2 months). I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). **Null cases reported. [†]Case series number a sum of category; however, excluded record not included in alive or dead total as entered as state DC not available or state DC available but no COD. [A]alive. [D]dead attributable and not attributed to this cancer diagnosis.

Research Question 3.2. "What are the differences in treatment administered among congenital AML, congenital ALL, infant AML, and infant ALL during this period?" To address Research Question 3.2, the infants diagnosed AL were evaluated as group (A-AL) using descriptive statistics stratified by treatment type administered using SEER codes radiation sequence with surgery, reason no cancer directed surgery, radiation recode, chemotherapy recode yes/no/unknown, chemotherapy administered and chemotherapy not administered, beam radiation administered, radiation NOS method or source not specified, radiation recommended unknown if administered, and beam radiation not administered (see Table 50).

An evaluation of treatment administered in the case series included (a) chemotherapy administered (290, 89.2%), (b) chemotherapy not administered (35, 10.8%), (c) beam radiation administered (12, 3.69%), (d) radiation NOS method or source not specified (1, 0.30%), (e) radiation recommended unknown if administered (1, 0.30%) and (f) beam radiation not administered (311, 95.7%).

The question was addressed further using descriptive statistics of leukemia groups stratified by treatment administered (see Table 50). The cases were divided into AML, ALL, ALAL, or OAL. The AML, ALL, ALAL, and OAL groups were subsequently divided by age at diagnosis, congenital (birth to < 2 months) or infant leukemia (≥ 2 to < 12 months). The chi-square test was used to evaluate the association between the treatment administered (chemotherapy or beam radiation) and lineage age group. An evaluation of treatment administered and lineage age group using the chi-square test =X^2 = 37.45, p = <.05. The null hypothesis of the test was treatment type administered would be significantly related to leukemia group diagnosed. There was a statistically significant relationship between treatment administered and lineage age group.

Table 50
The Treatments Administered to 325 Infants with Acute Leukemia from the SEER Database, 2008-2014

	Treatments administered	
	Yes *N* (% of A-AL)	No/Unknown *N* (% of A-AL)
Chemotherapy administered	290 (89.2%)	35 (10.8%)
Beam Radiation administered	12 (3.69%)	311 (95.7%)
Radiation, NOS method or source not specified	1 (0.30%)	**
Recommended, unknown if administered	1 (0.30%)	**

Note. Chi square (α =.05). Treatment vs. lineage-age group = X^2 = 37.45, p = < .05. N = 325. AL = acute leukemia. ** = Null cases reported.

The question was addressed further using descriptive statistics of the case series stratified by chemotherapy and radiation administered. The radiation administration was divided into beam radiation administered (12, 3.70%) or beam radiation not administered (311, 95.7%; see Figure

28). The majority, nearly all cases, were not administered beam radiation. The chemotherapy administration was divided into chemotherapy administered (290, 89.2%) or chemotherapy No/unknown (35, 10.8%; see Figure 29).

To further address Question 3.2, the C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL groups were subsequently divided by treatment type administered (see Table 51, Table 52, Table 53, Table 54, Table 55, Table 56, Table 57, and Table 58).

The C-AML diagnoses (34) treatment administered included chemotherapy administered (22, 64.7%) or chemotherapy not administered (12, 35.2%); there were no infants administered beam radiation, and this group was subclassified as no radiation and/or cancer directed surgery (34, 100%; see Table 51).

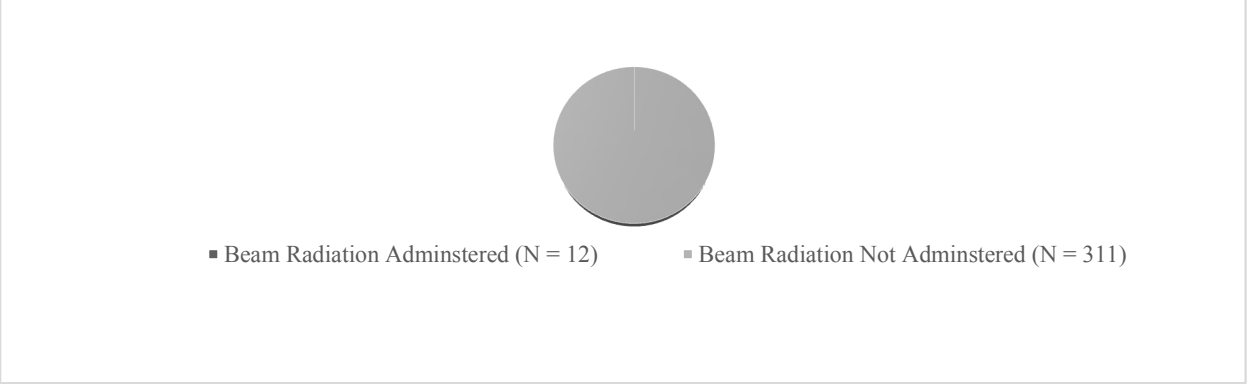


Figure 28. Radiation administration to 325 infants with acute leukemia. Radiation administered to 325 infants with congenital/infant leukemia diagnosed under 12 months of age from the SEER database, 2008–2014.

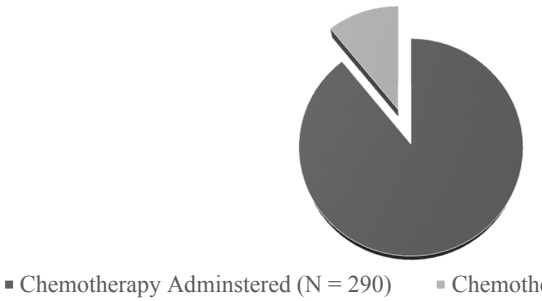


Figure 27: Treatments administered to 325 infants with congenital/infant leukemia diagnosed ≤ 12 months of age from the Surveillance, Epidemiology, and End Results (SEER) database, 2008–2014.

Figure 29. Chemotherapy administration to 325 infants with acute leukemia. Treatments administered to 325 infants with congenital/infant leukemia diagnosed under 12 months of age from the SEER)database, 2008–2014.

Table 51
The Treatments Administered to 34 Infants with Congenital Acute Myeloid Leukemia from the SEER Database, 2008-2014

	Treatments administered	
	Yes *N* (% C-AML)	No/Unknown *N* (% C-AML)
Chemotherapy administered	22, 64.7%	12, 35.2%
Beam Radiation administered	**	**
No radiation and/or cancer-directed surgery	34 (100%)	**
Radiation, NOS method or source not specified	**	**
Recommended, unknown if administered	**	**

Note. *N* = 34. C-AML = congenital acute myeloid leukemia (birth to ≥ 2 months). **Null cases reported.

The C-ALL diagnoses (18) treatment administered included chemotherapy administered (17, 94.4%) or chemotherapy not administered (1, 0.56%); there were no infants administered

beam radiation and this group was subclassified as no radiation and/or cancer directed surgery (18, 100%; see Table 52).

Table 52
Treatments Administered to 18 Infants with Congenital Acute Lymphoid Leukemia by from the SEER database, 2008-2014

	Treatments administered	
	Yes *N* (% C-ALL)	No/Unknown *N* (% C-ALL)
Chemotherapy Administered	17 (94.4%)	1 (0.56%)
Beam Radiation Administered	**	**
No radiation and/or cancer-directed surgery	18 (5.54%)	**
Radiation, NOS method or source not specified	**	**
Recommended, unknown if administered	**	**

Note. *N* = 18. C-ALL = congenital acute lymphoid leukemia (birth to < 2 months). **Null cases reported.

The C-ALAL diagnoses (2) treatment administered included chemotherapy administered (1, 50.0%) or chemotherapy not administered (1, 0.50%); there were no infants administered beam radiation and this group was subclassified as no radiation and/or cancer directed surgery (2, 100%; see Table 53).

Table 53
The Treatments Administered to Two Infants with Congenital Ambiguous Lineage Acute Leukemia from the SEER Database, 2008-2014

	Treatments administered	
	Yes *N* (% C-ALAL)	No/Unknown *N* (% C-ALAL)
Chemotherapy administered	1 (50.0%)	1 (50.0%)
Beam Radiation administered	**	2 (100%)
No radiation and/or cancer-directed surgery	2 (100%)	**
Radiation, NOS method or source not specified	**	**
Recommended, unknown if administered	**	**

Note. *N* = 2. C-ALAL = congenital ambiguous lineage acute leukemia (birth to ≥ 2 months). ** Null cases reported.

The C-OAL diagnoses (5) treatment administered included chemotherapy administered (3, 60.0%) or chemotherapy not administered (2, 40.0%); there were no infants administered beam radiation and this group was subclassified as no radiation and/or cancer directed surgery (5, 100%; see Table 54).

Table 54
The Treatments Administered to Five Infants with Congenital Other Acute Leukemia from the SEER Database, 2008-2014

Treatments administered		
	Yes *N* (% C-OAL)	No/Unknown *N* (% C-OAL)
Chemotherapy administered	3 (60%)	2 (40%)
Beam Radiation administered	**	5 (100%)
No radiation and/or cancer-directed surgery	5 (100%)	**
Radiation, NOS method or source not specified	**	**
Recommended, unknown if administered	**	**

Note. *N* = 5. C-OAL = congenital other acute leukemia (birth to ≥ 2 months). **Null cases reported.

The I-AML diagnoses (113) treatment administered included chemotherapy administered (104, 92.0%) or chemotherapy not administered (12, 10.6%); there were no infants administered beam radiation and this group was subclassified as no radiation and/or cancer directed surgery (34, 100%; see Table 55).

Table 55
The Treatments Administered to 113 infants with Infant Acute Myeloid Leukemia from the SEER Database, 2008-2014

	Treatments administered	
	Yes *N* (% I-AML)	No/Unknown *N* (% I-AML)
Chemotherapy administered	104 (92.0%)	9 (8.0%)
Beam Radiation administered	4 (3.54%)	108 (95.6%)
No radiation and/or cancer-directed surgery	113 (100%)	**
Radiation, NOS method or source not specified	**	**
Recommended, unknown if administered	**	**

Note. *N* = 113. I-AML = infant acute myeloid leukemia (≥ 2 months to < 12 months). **Null cases reported.

The I-ALL diagnoses (141) treatment administered included chemotherapy administered (133, 94.3%) or chemotherapy not administered (8, 5.7%); there were no infants administered beam radiation and this group was subclassified as no radiation and/or cancer directed surgery (136, 96.5%) and recommended and unknown if administered (see Table 56).

Table 56
The Treatments Administered to 141 Infants with Infant Acute Lymphoid Leukemia from the SEER Database, 2008-2014

	Treatments administered	
	Yes *N* (% I-ALL)	No/Unknown *N* (% I-ALL)
Chemotherapy administered	133 (94.3%)	8 (5.7%)
Beam radiation administered	4 (2.8%)	136 (96.5%)
No radiation and/or cancer-directed surgery	136 (96.5%)	**
Radiation, NOS method or source not specified	**	**
Recommended, unknown if administered	1 (0.70%	**

Note. *N* = 141. I-ALL = infant acute leukemia (≥ 2 months to < 12 months). **Null cases reported.

The I-ALAL diagnoses (10) treatment administered included chemotherapy administered (9, 90.0%) or chemotherapy not administered (1, 10%); there were no infants administered beam radiation and this group was subclassified as no radiation and/or cancer directed surgery (10, 100%; see Table 57).

Table 57
The Treatments Administered to 10 Infants with Infant Ambiguous Lineage Acute Leukemia from the SEER Database, 2008-2014

	Treatments administered	
	Yes *N* (% I-ALAL)	No/Unknown *N* (% I-ALAL)
Chemotherapy administered	9 (90%)	1 (10%)
Beam radiation administered	3 (30%)	7 (70%)
No radiation and/or cancer-directed surgery	10 (100%)	**
Radiation, NOS method or source not specified	**	**
Recommended, unknown if administered	**	**

Note. N = 10. I-ALAL = infant ambiguous lineage acute leukemia. **Null cases reported.

The I-OAL diagnoses (2) treatment administered included chemotherapy administered (1, 50.0%) or chemotherapy not administered (1, 50%); there were no infants administered beam radiation and this group was subclassified as no radiation and/or cancer directed surgery (20, 100%; see Table 58).

Table 58
The Treatments Administered to Two Infants with Infant Other Acute Leukemia from the SEER Database, 2008-2014.

Treatments administered		
	Yes (% I-OAL)	No/Unknown (% I-OAL)
Chemotherapy administered	1, 50.0%	1, 50.0%
Beam radiation administered	1, 50.0%	1, 50.0%
No radiation and/or cancer-directed surgery	2, 100%	**
Radiation, NOS method or source not specified	**	**
Recommended, unknown if administered	**	**

Note. $N = 2$. I-OAL = infant other acute leukemia (≥ 2 months to < 12 months). ** Null cases reported.

Summary

An evaluation of a retrospective case series in this dissertation study has provided documentation of patient and population demographics that can assist in the diagnosis of acute leukemia in infants less than 12 months of age. The findings of this dissertation study document the demographic and pathology data available from the NCI SEER database for a case series of 325 infants less than 12 months of age diagnosed with congenital and infant acute leukemia. This study is the first use of the NCI SEER database, a U.S. population cancer registry to describe specific age and leukemia lineage stratified subgroups of congenital and infant leukemia.

Chapter 5: Discussion

Introduction to the Chapter

The purpose of this dissertation study was to create a detailed report of acute leukemia in the less than 12 months of age population through investigation of its demographics, development, presentation, and elucidate further characteristics to drive classification of the disease. This dissertation study is based on the early misclassification of acute leukemia in young children during the mid-1900s, and the investigator sought to address the differences between the outcome of infants versus children with the disease. Since its identification, infant leukemia has maintained its place as a perplexing clinical issue in pediatric hematology oncology. There is a small amount of literature about infant leukemia, but this literature is plagued by a lack of differentiation between the ages of the children at diagnosis and has failed to address the distinctive properties that could clearly differentiate childhood disease from that in adults. Indeed, Dr. Arthur F. Abt proclaimed in 1937 that "the diagnosis of leukemia in infancy or children should offer no particular difficulty when one is confronted with a case presenting with the classical symptoms and signs of this condition," but quickly conceded when he presented "a group of cases which have been of interest and offered differential problems in personal experience" (p. 89). Yet, these cases and many more like them have set the stage for the need to drive scientific nosology classifications to document entities with distinct characteristic symptoms and natural histories in order to enhance the care of patients via ontology, a study that continues today and is an aim of this dissertation study. To identify these unique characteristics, describe disease entities, and subsequently classify them, research into the causative factors responsible for disease development driven by the sufficient-component cause model presented investigations into acute leukemia development in children less than 12 months, demonstrating

the clinical presentation of disease over the last 100 years; however, these factors were further investigated in this dissertation study. By linking biomedical, epidemiologic, pathologic, and health status into research on clinical outcomes, the application of integrative molecular pathology epidemiology (I-MPE) to a retrospective case series has identified the demographic, socio-economic, and clinical pathologic characteristics associated with tumor initiation and/or progression and has supported a role for interplay between these factors that influences infant leukemia disease etiology and prognosis. Interweaving the results of the retrospective case series with the social ecology theory showed the relationships between the social, institutional, and cultural contexts of individual-environment interactions and can subsequently be applied to advancing health care initiatives through updated laboratory interventions in pediatric hematology-oncology that are appropriately targeted for maximum impact to patient care. The application of previous findings and these theories were the aims of this dissertation study and are discussed in the following chapter.

The research investigations of this dissertation study were used to provide a comprehensive report of the less than 12 months of age population diagnosed with acute leukemia in the US using a SEER case series from 2008 to 2014. This chapter describes the findings of this dissertation study that evaluated the differences and similarities of age stratified lineage-specific acute leukemia, including demographics, pathologies, socio-economic characteristics, treatment, and outcomes of infants with records deposited in the SEER registry over this six-year period. A discussion of the implications of these findings on diagnostic laboratory algorithms in clinical practice, the limitations and delimitations of the dissertation study, and implications for further research for this population follows.

Discussion and Interpretation of Results

The development and presentation of leukemia in infants is diverse, and as the precision medicine model touts, “every disease is unique to the patient” (NCI, 2013, p. 11). However, understanding the basic underpinnings of disease pathologies is key to disease recognition, classification, and appropriate access to treatment for these infants. Leukemia classifications can be transformed through multiple rounds of refinement of the characteristics associated with a given disease. Categorizing and classifying these characteristics is used to broaden the search for influential factors and identify “pieces of the puzzle” necessary for leukemia development. However, how genetics, inheritance, environment, and socio-economic factors influence outcomes for these patients are dynamic and how best to ensure access to diagnostic, prognostic, and follow-up testing must be based on strict guidelines that can ensure all infant acute leukemia is identified appropriately to allow for timely and effective therapeutic intervention.

Case Series Summary

The case series was evaluated as a group to ensure appropriate classification in the SEER registry before proceeding to the research questions. The final case series of 325 records of acute leukemia extracted from the SEER registry resulted in eight diverse age and lineage stratified leukemia groups. The four major groups, ALL, AML, ALAL, and OAL, were composed of two smaller groups based on patient age at diagnoses and congenital or infant designations. Consistent with previous epidemiological data, the largest group included I-ALL with 141 diagnoses, followed by I-AML with 113 diagnoses, over the six-year period (Brown, 2013). I-ALL and I-AML combined accounted for 80% of cases of infant leukemia in this case series with the lineage groups with the least classification data, ALAL and OAL, and those occurring in the youngest infants (congenital groups combined) accounting for the remaining 20% of cases. These results indicated that a minority of infant leukemia diagnoses occurred in the youngest of

infants (birth to < 2 months of age) and groups that contained ambiguous lineage and other leukemia groups.

Of the infant acute leukemia, ALL dominated the diagnoses, followed by AML, ALAL, and OAL. In the I-AL group, ALL accounted for only 10% more diagnoses than AML, whereas I-ALAL and I-OAL diagnoses accounted 1/14 and 1/70 of the diagnoses in the I-AL group, making them exceedingly rare findings in diagnostics. In comparison, AML dominated the diagnoses in the congenital acute leukemia group (C-AL). In the C-AL group, C-AML accounted for approximately 50% more diagnoses than ALL, whereas C-ALAL and C-OAL diagnoses accounted for 1/17 and one seventh of the diagnoses in the C-AL group, making them exceedingly rare findings in diagnostics.

The registry reporting sources and diagnostic methodologies of cases included in the SEER registry can affect the findings of this dissertation study through appropriate and inappropriate classification of acute leukemia cases included in this case series. However, there was great similarity in the types of reporting sources for all diagnoses. This finding indicated there was uniformity in registry reporting sources in the routine transfer of case data to the SEER registry, making errors in the process unlikely. The majority of the case series (97.2%) were diagnosed in a hospital inpatient/outpatient or clinic. This finding was consistent with the known presentation of infant acute leukemia, a condition in which infants are more likely to present urgently in an emergency department rather than in a non-urgent setting, such as the pediatrician's office (Guenova & Balatzenko, 2013; Naeim, Rao, Song, & Grody, 2018).

The majority of cases included in the case series underwent standard laboratory-based methodologies used for the classification of neoplasms that included microscopic confirmation of morphology; the visual appearance of the neoplasm, including identification of the leukemia

cell line; and the stage of differentiation. These findings correlated with standard American Society for Hematology (ASH) and College of American Pathologists (CAP) recommendations for the diagnosis of acute leukemia, which include (a) a review of complete blood counts, (b) leukocyte differentials, (c) evaluation of a peripheral blood smear, and (d) follow on testing of a bone marrow aspirate smear via morphologic evaluation in patients with a suspected leukemia (95.4% of case series; Arber et al., 2017). In addition to the requirements for morphologic assessment, additional specimens must be collected to ensure reflex testing for lab testing/marker and cytochemical studies are made available, and in practice, these tests may be performed simultaneously to ensure cases without or conflicting morphological findings are still diagnosed appropriately by the clinical service (Arber et al., 2017). With the majority of cases diagnosed via a microscopically confirmed methodology, the diagnostic confirmation modalities were dominated by positive histologic studies only (76.6%) and cases in which no further reflex testing was used to confirm the leukemia. As aligned to ASH and CAP guidance, approximately 20% of cases were reported to have positive histology combined with immunophenotyping and/or positive genetic studies. This finding may represent either limited diagnostic workup of query leukemia specimens and/or a lack of informative immunophenotyping/genetic studies (Arber et al., 2017). In this case series, the use of informative genetic testing was entered into the SEER record in under 3% of cases even though standard guidance have suggested further diagnostic testing. There were no informative markers that allowed for classification of the many patients in the case series using positive genetic studies even though the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017* classification relies heavily on these findings to define subgroups and subtypes of leukemia (Arber et al., 2017). This factor may indicate most cases were evaluated with positive histology and immunophenotyping more often

than positive histology with immunophenotyping and positive genetic studies. However, all studies underwent laboratory investigations to confirm the suspicion of acute leukemia. Yet, a minority of cases did not undergo these well established and standard laboratory diagnoses, which represents subsequent reflex laboratory/marker studies that indicated the presence of leukemia (2.2% of cases), and clinical diagnoses only had limited access of diagnostic sample to appropriate workup (0.3%) in the case series. These findings may be reflected in the other acute leukemia subgroup defined by the inability to further characterize the leukemia into a WHO 2017 subgroup or subtype.

Research Questions

There is a distinctive clinical presentation of children diagnosed with congenital and infant acute leukemia under 12 months of age in the SEER database over the six-year period between 2008 to 2014 in the United States with a unique epidemiological profile of age and leukemia subtype stratified groups of AML, ALL, ALAL, and OAL documented in this case series.

AML. The A-AML group, including all diagnoses less than 12 months in the case series, composed roughly one half of all cases (45.2%) in the case series, which was consistent with previous epidemiological studies of infant acute leukemia (Bresters et al., 2002; Heerema et al., 1994). Within the A-AML group, diagnoses in the older group of children aged 2 months or more to less than 12 months dominated with fewer cases in the birth to less than 2 months of age group (I-AML 76.8% vs. 23.1% C-AML). A-AML diagnoses are variable in age and occurred in all estimated age at diagnosis month groups in both C-AML and I-AML. AML diagnosed in those aged 2 months or more to less than 12 months are more common in the less than 12 months population with fewer cases in those from birth to less than 2 months. The I-AML cases

accounted for one third (34.7%) of all diagnoses within the case series, and C-AML accounted for a mere 10.4% of A-AL. The diagnoses in every age group between birth to less than 12 months of age was documented with a large variability in the number of infants in each group with a range of a few (4 cases) to numerous diagnoses (24) across the series. This finding of additional cases of I-AML and fewer cases of C-AML was confirmed through quantification of the variability in the population represented by a mean age of diagnoses of nearly 6 months (5 months 24 days of age) with a large standard deviation (5.8 ± *SD* 3.8). There are distinct trends between C-AML and I-AML groups for estimated age at diagnosis. In combination, these findings indicated AML diagnoses occurred either shortly after birth or just before a child's first birthday in the birth to less than 12 months of age group. A child with AML between birth to less than 2 months of age is most likely to be diagnosed in the period from birth to less than 1 month of age rather than closer to 2 months of age. This finding may represent the known association of congenital acute leukemias with in utero development or congenital anomalies associated with an increased risk of AML development presenting shortly after birth as confirmed by previous studies using retrospective analysis of Guthrie cards or other unidentified risk factors for leukemia development combined with access or proximity to health care professionals in this stage of life (M. Greaves, 2005). Conversely, a child with AML between 2 months or more to less than 12 months is most likely to be diagnosed in the period from 11 months or more to less than 12 months of age. The findings of this case series showed that AML in the infant populations is a rare entity and are consistent with previous reports that indicated there was an increased incidence of AML in pediatric patients aged 1 to 4 years with fewer diagnoses in those less than 12 months of age, but it is the most common acute leukemia in the congenital infant population (Barrington-Trimis et al., 2017).

The sex of infants in the A-AML group included more males (78) versus females (69) diagnosed for a M/F ratio of 1:0.88. Males were more likely to be diagnosed with AML in the A-AML less than 12 months of age group as found in 146 infants, 46.9% versus 53.1% male diagnoses. This finding was the same finding as ALL and ALAL diagnoses, but the opposite of OAL as discussed later in this chapter.

There were major differences between race and ethnicity groups of A-AML, which may represent the race and ethnicity composition of SEER registry areas and the U.S. population but also has supported differences between acute leukemia lineage groups. The A-AML diagnoses stratified by race and ethnicity indicated the majority of diagnoses occurred in the Caucasian (White) infant race group; the highest number was in the non-Hispanic ethnicity, followed by Hispanic Caucasian (White) infants. The findings of this case series showed that Caucasian infant populations were most likely to be diagnosed with AML and were consistent with previous reports that suggested AML diagnoses are dominated by Caucasian infants rather than other races in the U.S. and global populations (Barrington-Trimis et al., 2017; Brown, 2009). There were 110 diagnoses in Caucasian (White) infants that accounted for 74.8% of A-AML diagnoses with the majority diagnosed in non-Hispanic Caucasian (65, 31.8%) followed by Hispanic Caucasian (White; 45, 40.9%) infants. Caucasian (White) infants were more likely than Hispanic and non-Hispanic African-American (Black; 14.9% of A-AML), Asian or Pacific Islander (7.5% of A-AML), American Indian or Alaska Native (0.68% of A-AML), and unknown race (2.04% of A-AML) infants to be diagnosed with AML less than 12 months of age. Diagnoses in African-American (Black) infants (22 cases) were 80% less than the number of diagnoses in Caucasian (White) infants (110 cases). Within the African-American (Black) group, non-Hispanic infants composed the majority of cases (90.9%) versus African-American (Black)

Hispanic infants (9.09%). The third group, cases documented in Asian or Pacific Islander races, composed 11 diagnoses with the majority of the cases documented in non-Hispanic (90.9%) versus Hispanic infants (9.09%). The smallest group, the combined American Indian or Alaskan Native group, recorded a single case in a non-Hispanic infant. There were three cases within the A-AML group that were coded without a race and/or designated unknown but were designated as non-Hispanic ethnicity. These findings indicated the collection of race and ethnicity information can be applied to guide diagnostic testing in infants with a query leukemia presentation.

All 147 cases in the A-AML group were placed into the acute myeloid leukemia and related neoplasms group, which composed approximately half (45.7%) of A-AL diagnoses in the case series. This finding was surprising as previous studies have indicated the majority of acute leukemia diagnoses in infants are AML and not a near equal number to ALL as reported herein (Bresters et al., 2002; Morse et al., 1979; Resnik & Brod, 1993; Wolk et al., 1974). Three of the four subgroups of the acute myeloid leukemia and related neoplasms group were observed in the case series with the majority of cases (131, 40.3%) designated into AML not otherwise specified, accounting for 89.1% of the A-AML, 22.4% of the C-AML, and 89.3% of the I-AML diagnoses. This finding indicated that nearly 90% of AML diagnoses in the case series were assigned to a not otherwise specified subgroup reserved for diagnostic cases without specific genetic features of another ICD-O-3/WHO 2017 group. There were no observations of the therapy-related myeloid neoplasms subgroup and subtype. This finding was consistent with the young age of the patient case series as patients less than 12 months of age were unlikely to have been diagnosed with a primary cancer and subsequently present before their first birthday with a secondary therapy-related neoplasm resulting from the therapeutic chemotherapy for the first neoplasm. This finding was promising for infants diagnosed with other cancer types that are diagnosed with

a secondary neoplasm, resulting from chemotherapy in the first year of life, which is extraordinarily rare.

The AML not otherwise specified subgroup includes 10 subtypes that are based on the presence and/or absence of specific lineage markers to determine the diagnosis. These findings of the case series have confirmed that the majority of A-AML diagnoses occurred without genetic testing confirmation aligned to an ICD-O-3/WHO 2017 group. In this case series, nine of the 10 subtypes were observed with an 11th subtype designated in this dissertation study that is not a WHO 2017 defined subtype: myeloid leukemia, NOS. There were no designations of pure erythroid leukemia or acute basophilic leukemia in the case series. These diagnoses are based on morphology and/or immunophenotyping data without the need for specific genetic studies to confirm the diagnoses. Genetic studies are not necessary to confirm these diagnoses but may still be performed to confirm a diagnosis given genetic studies for other AML groups are exclusive to those leukemia subgroup diagnoses, but this information was not indicated in the SEER registry records. The AML not otherwise specified subgroup was dominated by cases (61, 18.8%) in which no further stratification could be concluded with the given studies, and the subtype AML not otherwise specified accounted for 41.5% of the A-AML group, 44.1% of the C-AML and 40.7% of the I-AML diagnoses.

The remaining AML diagnoses in the case series were dominated by the subgroups (a) acute monoblastic and monocytic leukemia, (b) acute megakaryoblastic leukemia, and (c) acute myelomonocytic leukemia. These findings of the acute monoblastic and monocytic leukemia, acute megakaryoblastic leukemia, and acute myelomonocytic leukemia subgroups in this case series were consistent with previous studies that suggested 70% of infants with AML have monoblastic, myelomonocytic, or megakaryoblastic leukemia; however, in this case series, these

groups accounted for only approximately 40% of diagnoses (Masetti et al., 2015; Naeim et al., 2018; Webb et al., 2001). This finding may reflect evolution of the ICD-O-3/WHO 2017 classifications that have emerged since these previous reports on this population. Previous reports of infant acute leukemia not previously classified may now be classified into new groups not included in previous WHO or FAB classifications. Acute monoblastic and monocytic leukemia accounted for approximately one fifth of A-AML in the case series, and this finding was consistent with known incidence of this subtype as one of the most common types of AML in young children (Masetti et al., 2015; Naeim et al., 2018). Acute monoblastic and monocytic leukemia or the previously designated FAB type M5 was observed in 28 diagnoses and accounted for 8.6% of A-AL, 19.0% of the A-AML, 11.8% of the C-AML, and 21.6% of the I-AML diagnoses. Acute megakaryoblastic leukemia accounted for approximately one fifth of A-AML in the case series and has been reported previously to have a higher incidence in the young infant population, and it is known to represent approximately 1% of leukemias throughout childhood, but it is most common in children with Down syndrome, a congenital predisposing factor (Naeim et al., 2018; Verschuur, 2004). Acute megakaryoblastic leukemia or the previously designated FAB type M7 was observed in 26 diagnoses and accounted for 7.7% of A-AL, 17.7% of the A-AML group, 20.6% of the C-AML, and 12.9% of the I-AML diagnoses. Acute myelomonocytic leukemia was more likely to be diagnosed in older children (≥ 2 months to < 12 months), but not younger infants (birth to < 2 months) in the case series. Acute myelomonocytic leukemia or the previously designated FAB type M4 accounted for 1.8% of all A-AL, 4.08% of the A-AML group, no diagnoses in C-AML, and 5.4% of the I-AML diagnoses.

The AML not otherwise specified subgroup included a minority of cases in the other subtypes: (a) AML with minimal differentiation; (b) AML with maturation; (c) AML without

maturation; (d) acute panmyelosis with myelofibrosis; and (e) myeloid leukemia, NOS. AML with minimal differentiation accounted for approximately 3% of A-AML with near equal diagnoses in C-AML and I-AML groups in the case series and was consistent with known incidence of this subtype as accounting for 5% or more of AML cases, mostly in the infant or older adult populations (Barbaric et al., 2007). AML with minimal differentiation accounted for 1.2% of A-AL, 2.72% of the A-AML, 2.9% of the C-AML, and 2.7% of the I-AML diagnoses. AML with maturation accounted for approximately 2% of A-AML in the case series and was consistent with known incidence of this subtype as accounting for approximately 10% of all AML cases, which is most common in children 2 years of age or more as confirmed by the small number diagnosed in this case series limited to children less than 12 months of age (Barbaric et al., 2007; Naeim et al., 2018). AML with maturation accounted for 0.92% of A-AL, 2.04% of the A-AML, 2.9% of the C-AML, and 1.8% of the I-AML diagnoses. AML without maturation was a very rare finding in this dissertation study and was consistent with known incidence of this subtype as accounting for approximately 10% to 15% of all AML cases (Naeim et al., 2018). AML without maturation accounted for 0.30% of A-AL, 0.68% of the A-AML, no diagnoses in C-AML, and 0.90% of the I-AML diagnoses. Acute panmyelosis with myelofibrosis is an exceedingly rare leukemia, accounting for less than 1% of all AML with rare case reports of fatal familial infantile myelofibrosis as a congenital leukemia, and the findings of this case series have confirmed these findings with APMF accounting for 0.30% of A-AL, 0.68% of the A-AML, 2.9% of the C-AML diagnoses, and no diagnoses in I-AML group (Naeim et al., 2018; Sheikha, 2004). The non-WHO 2017 defined category used in the SEER registry in the absence of other classification criteria and myeloid leukemia, NOS accounted for 0.30% of acute leukemia, 0.68%

of the A-AML group, no diagnoses in C-AML, and 0.90% of I-AML diagnoses, which is consistent with the rare use of this category in the SEER registry.

A very small number of AML cases were classified using genetic testing. Less than 5% (4.6%) of cases in the acute myeloid leukemia and related neoplasms group were placed into the subgroup acute myeloid leukemia with balanced translocations/inversions subgroup, which included 11 subtypes that were based on the presence and/or absence of specific cytogenetic or molecular genetic abnormalities to determine the diagnosis. In this case, 4 of the 11 subtypes were observed. There were no designations of "AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*," "AML with t(6;9)(p23;q34.1); *DEK-NUP214*," "AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*," "AML with *BCR-ABL1*," or the acute myeloid leukemia with gene mutations subtypes: (a) AML with mutated *NPM1,* (b) AML with biallelic mutations of *CEBPA*, and (c) AML with mutated *RUNX1* in the case series. The findings of this case series were consistent with known reports of these leukemia subtypes, including "AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1,*" which is known to account for approximately 1% to 5% of acute leukemia, is primarily diagnosed in younger patients with a higher incidence in adults, and the absence of diagnostic cases in this infant case series has confirmed these previous findings (Swerdlow et al., 2017). "AML with t(6;9)(p23;q34.1); *DEK-NUP214*" has a known frequency of approximately 1% of childhood leukemia but is very rare in infants, and the absence of diagnostic cases in this infant case series has confirmed these previous findings (Swerdlow et al., 2017). "AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*" has a known frequency of approximately 1% to 2% of all AML and is primarily a finding in adult patients and not infants, and the absence of diagnostic cases in this infant case series has confirmed these previous findings (Swerdlow et al., 2017). "AML with *BCR-ABL1*"

accounts for less than 1% of all AML and is primarily a finding in adult patients and not infants, and the absence of diagnostic cases in this infant case series has confirmed these previous findings (Swerdlow et al., 2017). The acute myeloid leukemia with gene mutations subtypes were not documented in the case series, but this finding may represent a lack of genetic studies and/or overlapping morphology with another AML group or subgroup, and thus, these cases were not coded separately by SEER registrars. AML with mutated *NPM1* has a known frequency of approximately 2% to 8% of childhood AML with approximately 85% to 95% of cases consistent with a normal karyotype by cytogenetic studies with the other 5% to 15% consistent with numerous chromosomal aberrations; however, these secondary findings cannot be coded for in the SEER registry as they are not specific to WHO genetic subtypes, and it is possible that AML with mutated *NPM1* were present in the case series but coded with their morphology and immunophenotyping rather than genetic studies had these studies been performed at diagnosis (Swerdlow et al., 2017). AML with biallelic mutations of *CEBPA*, has a known frequency of approximately 4% to 9% of childhood AML with approximately 70% of cases consistent with a normal karyotype by cytogenetic studies, and the other 30% are consistent with numerous chromosomal aberrations; however, these secondary findings cannot be coded for in the SEER registry as they are not specific to WHO genetic subtypes, and it is possible that AML with biallelic mutations of *CEBPA* were present in the case series but coded as AML with maturation, acute myelomonocytic leukemia, or acute monoblastic and monocytic leukemia, given they also meet the morphology and immunophenotyping criteria for these groups rather than genetic studies had these studies been performed at diagnosis (Swerdlow et al., 2017). AML with mutated *RUNX1* is a provisional entity in the current WHO 2017 classification and has a known frequency of approximately 4% to 16% of AML with the highest frequencies in older adults and

has not been routinely observed in infants, and the WHO 2017 classification guides against categorizing AML into this group should they meet the criteria of other AML subgroups or subtypes. Given this information, genetic studies for *RUNX1* mutation status may have been performed on patients in the case series but not reported given the provisional nature of the entity, and/or the lack of patients with this subtype of AML, and the absence of diagnostic findings in this infant case series have confirmed these previous findings in the infant population.

C-AML in the case series were more likely to have been categorized using a genetic laboratory study with fewer cases of I-AML diagnosed with this methodology. Four of the 11 subtypes of acute myeloid leukemia with balanced translocations/inversions accounted for only 15 cases, 10.2% of the A-AML, 44.1% of C-AML, and 8.84% of I-AML. The AML with "t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL) variant *KMT2A* translocations in acute leukemia" subtype dominated the acute myeloid leukemia with balanced translocations/inversions subgroup with 11 diagnoses or 3.4% of A-AL, 7.5% of A-AML, 8.8% of C-AML, and 7.07% of I-AML. This finding was consistent but lower than previous reports of *KMT2A* translocations in infant acute leukemia. Previous reports have documented the highest incidence of *KMT2A* translocations in children with previous reports indicating over approximately 90% of infants less than 12 months of age have these abnormalities with over 120 different translocation partners identified to date (Bresters et al., 2002). The other infant AL groups with *KMT2A* translocations, A-ALL, and A-ALAL do not account for an anticipated, significantly higher number of diagnoses in the case series. Instead, if included as a group, this aberration accounted for under 5% (4.35%) of the case series, a finding in stark contrast to previous studies on the infant population. However, many *KMT2A* aberrations are cryptic and require specific cytogenomic studies. Aberration status may not have been evaluated for all patients in the case

series, and the diagnoses could overlap with other ICD-O-3/WHO 2017 groups or the diagnosis may have been coded incorrectly, but this finding may represent a true difference in the evaluation of the under 12 month of age population as previous studies that included older children and reported a higher frequency of *KMT2A* aberrations. Previous reports of *PML-RARA* translocations in acute leukemia reported the highest incidence in younger adults, and this finding was consistent with the findings of this case series (Chen, Kantarjian, Wang, Cortes, & Ravandi, 2012). APL with *PML-RARA* subgroup accounted for two diagnoses or 0.62% of A-AL, 1.36% of A-AML, 2.9% of C-AML, and 0.88% of I-AML. Previous reports of *CBFB-MYH11* translocations in acute leukemia indicated the highest incidence in younger adults with a median age of diagnosis of approximately 35 years (Poddighe et al., 2018). However, rare cases of *CBFB-MYH11* leukemia have been reported in utero without detection until 4 years of age with retrospective confirmation via Guthrie cards, a finding that indicated *CBFB-MYH11* may be present in this infant age group but present later outside of the diagnostic age group of this case series as confirmed by the findings of this case series (Poddighe et al., 2018). "AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*" accounted for a single diagnosis or 0.30% of A-AL, 0.68% of A-AML, no cases in C-AML, and 0.88% of I-AML. Previous reports indicated acute megakaryoblastic leukemia is a common subtype in the infant population, but the specific genetic subtype "AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*" has a known frequency of 0.8% of infant leukemia, which was confirmed by this case series, and is not documented in adults (Swerdlow et al., 2017). "AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*" accounted for a single diagnosis or 0.30% of A-AL, 0.68% of A-AML, 2.9% of C-AML, and no cases in I-AML. The final subgroup/subtype of AML with myelodysplasia-related changes (MRC) or AML-MRC is reported mainly in elderly patients and

is extremely rare in children as it is associated with patients with a previously diagnosed myelodysplastic syndromes (MDS) or MDS/myeloproliferative neoplasm (MPN), which is an unlikely occurrence in children less than 12 months of age as confirmed by this case series (Swerdlow et al., 2017). AML-MRC accounted for a single diagnosis or 0.30% of A-AL, 0.68% of A-AML, no cases in C-AML, and 0.88% of I-AML.

Infants with acute leukemia often present urgently to the emergency department or clinic and is generally not a secondary finding via laboratory only testing, but may only be detected after rapid progression and death as confirmed by the diagnostic reporting location findings of A-AML in this case series (Naeim et al., 2018). The A-AML group was dominated by diagnoses reported by a hospital inpatient/outpatient or clinic, which accounted for 97.9% of A-AL, 97.0% of C-AML, and 98.2% of I-AML. A mere fraction of cases were reported by only a laboratory, 2.94% of C-AML, and 1.76% of I-AML.

All cases within A-AML were evaluated for their disease primary site to ensure the diagnoses were consistent with AML and that they should be included in the cases series. The case series findings were consistent with the known variance across the US in the initial diagnostic workup of acute leukemia as recently addressed by CAP and ASH 2017 guidelines (Arber et al., 2017). All 147 cases included in the A-AML were coded as C42.1-bone marrow, a finding consistent with appropriately diagnosed AML (Naeim et al., 2018). Following the bone marrow evaluation, subsequent studies used for diagnostic confirmation methodology varied in the A-AML group but included positive histology, positive histology AND immunophenotyping, AND/OR positive genetic studies, positive exfoliative cytology, no positive histology; positive laboratory test/marker study; clinical diagnosis only; and unknown methodologies. Diagnoses in the case series were dominated by positive histology, which accounted for 115 diagnoses or

35.4% of A-AL, 78.2% of A-AML, 70.5% of C-AML, and 96.4% of I-AML. This finding was consistent with basic workup of leukemia patients using a trephine biopsy necessary for a diagnosis prior to initiating further reflex studies. The second largest group, accounting for only a fraction of the diagnostic confirmation methodologies, positive histology AND immunophenotyping AND/OR positive genetic studies accounted for 23 diagnoses or 7.07% of A-AL, 15.6% of A-AML, 14.7% of C-AML, and 15.9% of I-AML. This finding was consistent with ASH and CAP guidance for testing of leukemia patients necessary for a diagnosis prior to initiating further reflex studies. The remaining groups accounted for a small number of diagnoses, including positive exfoliative cytology, no positive histology, which accounted for 1.54% of A-AL, 3.4% of the A-AML, 5.88% of C-AML, and 2.65% of I-AML; positive laboratory test/marker study, which accounted for 0.61% of A-AL, 1.36% of the A-AML, 5.88% of C-AML, and no cases of I-AML; clinical diagnosis only, which accounted for 0.30% of A-AL, 0.68% of A-AML, 2.94% of C-AML, and no cases of I-AML; and unknown diagnostic confirmation methodology accounted for 0.30% of A-AL, 0.68% of the A-AML, no cases of C-AML, and 0.88% of I-AML.

These insurance status findings indicated the majority of AML cases were insured at diagnosis, primarily with private insurance, otherwise with Medicaid coverage, and a small number of patients were reported without insurance or documented insurance status. The insurance status of the A-AML group was dominated by insured patients, which accounted for 20.9% of A-AL, 46.2% of A-AML, 55.8% of C-AML, and 43.3% of I-AML. The insured/no specifics accounted for 3.69% of A-AL, 8.16% of A-AML, 8.82% of the C-AML, and 7.96% of the I-AML. These two groups of insured and insured/no specifics accounted for 24.6% of A-AL, 54.5% of A-AML, 64.6% of C-AML, and 51.3% of I-AML. The second largest group, any

Medicaid, accounted for 18.4% of A-AL, 40.8% of A-AML, 26.4% of C-AML, and 45.1% of I-AML. The insurance status unknown accounted for only 1.53% of A-AL, 3.4% of A-AML, 8.82% of C-AML, and 1.76% of I-AML. The last group of uninsured accounted for only 0.61% of A-AL, 1.36% of A-AML, no cases of C-AML, and 1.76% of I-AML.

ALL. The A-ALL group, including all diagnoses less than 12 months of age in the cases series, composed approximately half of all cases (48.9%) in the case series, which was consistent with previous epidemiological studies of infant acute leukemia with a slightly higher report of ALL not reported in previous studies (Bresters et al., 2002; Brown, 2013). Within the A-ALL group, diagnoses in the older group of children 2 months or more to less than 12 months of age dominated with fewer cases in the birth to less than 2 months of age group (I-ALL 88.7% vs. 11.3% C-ALL). The I-ALL cases accounted for one half of cases (43.3%) of A-AL, and C-ALL accounted for a mere 5.54% of A-AL. This finding was surprising for ALL in the older infant group as previous studies have indicated that acute leukemia diagnoses in children less than 12 months are dominated by AML with recurrent reporting of higher proportion of AML diagnoses than ALL, whereas in this case series, AML and ALL were observed in near equal numbers (Bresters et al., 2002; Brown, 2013). However, consistent with previous findings, ALL diagnosed in those aged 2 months or more to less than 12 months (I-ALL) were more common in the less than 12 month population with fewer cases in the birth to less than 2 months (C-ALL) in the case series (Bresters et al., 2002; Brown, 2013). This finding has confirmed previous reports that indicated AML dominates the diagnoses in the C-AL age group, not ALL (Bresters et al., 2002; Brown, 2013). There was a small range of age at diagnoses in the A-ALL group. Subdivision across all 12 months in the infant case series included diagnoses in every age group

between birth to less than 12 months of age with variability of only few cases (8) cases to over double the number of diagnoses (17) across the months of age in the series.

A-ALL diagnoses were variable in age and occurred in all estimated ages at diagnoses groups between C-ALL and I-ALL. This finding of more cases of I-ALL and fewer C-ALL was confirmed through quantification of the variability in the population represented by a mean age of diagnoses of 6 months (6 months, 6 days of age) with a large standard deviation (6.18 ± *SD*3.4). However, there were distinct trends in the C-ALL and I-ALL groups for estimated age at diagnosis. A child with C-ALL between birth to less than 2 months of age is most likely to be diagnosed in the period of age 1 month or more to less than 2 months rather than closer to birth as was observed in C-AML cases. This finding may represent the known association of congenital acute leukemias with in utero development and was consistent with the two-hit hypothesis for B-ALL that suggested a single prenatal genetic aberration requires a later secondary event, which is associated with delay and subsequent post-natal presentation with later detection for ALL rather than AML (Brown, 2013; Cao et al., 2016; Isaacs, 2003; Sanjuan-Pla et al., 2015).

Conversely, a child with ALL between 2 months or more to less than 12 months is most likely to be diagnosed in the period from 7 months or more to less than 8 months of age. However, diagnoses across 2 months or more to less than 12 months age group varied very little between the range of 10 to 18 diagnoses in each month of age. This finding was consistent with increased incidence of ALL in pediatric patients aged 1 to 4 years and fewer cases in those less than 12 months of age, and as previously reported, the number of ALL diagnoses in the case series increased as the age of the children increased (Barrington-Trimis et al., 2017).

The sex of infants in the A-ALL group included more males (92) versus females (67) diagnosed for a M/F ratio of 1:0.73. Males were more likely to be diagnosed with ALL in the A-ALL less than 12 months of age group as found in 159 infants: 42.1% female versus 58.8% male diagnoses. This finding was the same as AML and ALAL, but the opposite of OAL diagnoses discussed within this chapter.

There were major differences between race and ethnicity groups of A-ALL, which may represent the race and ethnicity composition of SEER registry areas and the U.S. population, but also had supported the differences between acute leukemia lineage age groups. The findings of this case series showed that Hispanic Caucasian infant populations are most likely to be diagnosed with ALL and were consistent with previous reports that suggested ALL diagnoses are dominated by Caucasian infants rather than other races in the U.S. and global populations (Brown, 2013). There were 116 diagnoses in Caucasian (White) infants, accounting for 73.0% of A-ALL diagnoses with the majority diagnosed in Hispanic Caucasian (60, 51.7%), followed by non-Hispanic Caucasian (White; 56, 48.2%) infants. This finding of the majority of diagnoses in Caucasians infants was similar to the findings in the A-AML group; however, unlike A-AML, A-ALL occurs more often in Hispanic rather than non-Hispanic Caucasian (White) infants. Comparatively, other groups accounted for fewer cases, including Hispanic and non-Hispanic African-American (Black; 10.7% of A-ALL), Asian or Pacific Islander (12.5% of A-ALL), American Indian or Alaska Native (1.89% of A-ALL), and unknown race (1.89% of A-ALL) infants to be diagnosed with ALL less than 12 months of age. Diagnoses in African-American (Black) infants (17) were approximately 85% less than the number of diagnoses in Caucasian (White) infants (116) cases. Within the African-American (Black) infant group, non-Hispanic infants composed the majority of cases (82.3%) versus African-American (Black) Hispanic

infants (17.6%). The third group, cases documented in Asian or Pacific Islander race infants, was composed of 18 diagnoses with the majority of the cases documented in non-Hispanic (90.0%) versus Hispanic infants (10.0%). The smallest groups, the combined American Indian or Alaskan Native infant race group and those that were coded without a race and/or designated unknown race, represented three cases within A-ALL, respectively. The American Indian or Alaskan Native infant group included only non-Hispanic infants, whereas the unknown group included cases reported as non-Hispanic (66.7%) and Hispanic (33.3%) infants. These findings indicated the collection of race and ethnicity information can be applied to guide diagnostic testing in infants with a query leukemia presentation.

All 159 cases in the A-ALL group were placed into the acute lymphoid leukemia and related neoplasms group, which composed approximately half (49.4%) of all AL diagnoses in the case series. Three of the four subgroups of the acute lymphoid leukemia and related neoplasms group were observed in the case series with the majority of cases (123, 37.8%) designated in B-lymphoblastic and leukemia/lymphoma, NOS, accounting for 77.3% of the A-ALL, 94.4% of the C-ALL, and 75.7% of the I-ALL diagnoses. This subgroup/subtype was not further divided in the *WHO 2017 Classification of Precursor Lymphoid Malignancies*. This finding indicated that nearly 80% of ALL diagnoses in the case series were assigned to a not otherwise specified subgroup reserved for diagnostic cases without specific features of another ICD-O-3/WHO 2017 group. These diagnoses were based on morphology and/or immunophenotyping data without the need for specific genetic studies to confirm the diagnoses. Genetic studies are not necessary to confirm these diagnoses, but testing may still be performed to confirm a diagnosis given genetic studies for other ALL groups are exclusive to those leukemia subgroup diagnoses and may present cryptically in genetic testing without other supporting evidence. There is a slightly

reduced proportion (80% vs. 90%) in the not otherwise specified group for ALL and AML, respectively, which may represent the newly emerged ALL genetic subgroups found in the WHO 2017, but not WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008. There were no observations of the NK cell lymphoblastic leukemia/lymphoma subgroup and subtype, and this finding was consistent with the known difficulty to define and recognize this rare entity in all patients (Swerdlow et al., 2017).

I-ALL in the case series were more likely to have been categorized using a genetic laboratory study with fewer cases of C-ALL diagnosed with this methodology. The second largest group (15.0% of cases) in the acute lymphoid leukemia and related neoplasms group were placed into the subgroup B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities subgroup, which accounted for 5.55% of C-ALL and 16.3% of I-ALL. In this case series, only four of the nine subtypes of the B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities subgroup were observed.

There were five of the nine subtypes of B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities not observed in this case series. It is important to recognize these negative findings in the infant acute leukemia population as they are unlikely to be detected during diagnostic workup and laboratory algorithms may be adjusted based on this information. There were no designations of "B-lymphoblastic and leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1*," "B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*," "B-lymphoblastic and leukemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3*," "B-lymphoblastic and leukemia/lymphoma, *BCR-ABL1-like*," or "B-lymphoblastic and leukemia/lymphoma with iAMP21" in the case series. These findings were consistent with known reports of these leukemia subtypes, including "B-lymphoblastic and

leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1*" and was known to account for approximately 25% of adult ALL, but only 2% to 4% of childhood cases, and previous reports included infants and older children. Results of this infant case series were consistent and did not include diagnoses of this subtype (Swerdlow et al., 2017). "B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*" accounted for 25% of childhood leukemia, but is not seen in infants, and this finding was confirmed by this dissertation study (Swerdlow et al., 2017). "B-lymphoblastic and leukemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3*" has a known frequency of under 1% of A-ALL, and the findings herein are consistent as it was not documented in this infant case series (Swerdlow et al., 2017). "B-lymphoblastic and leukemia/lymphoma, *BCR-ABL1-like*" accounted for 10% to 25% of all ALL and has the lowest frequency during childhood (Swerdlow et al., 2017). With standard cytogenetic risk, childhood ALL has a higher frequency of *BCR-ABL1-like,* and the known risk factors in adolescent and adult groups included Native American genetic ancestry and Hispanic ethnicity, but there are no previously documented factors in the infant population for this subtype. The "B-lymphoblastic and leukemia/lymphoma, *BCR-ABL1-like*" subgroup was not documented in this case series; however, genetic studies for *BCR-ABL1-like* status may have been performed for patients in the case series, but not reported, given the provisional nature of the entity and/or the lack of patients with this subtype of ALL (Swerdlow et al., 2017). B-lymphoblastic and leukemia/lymphoma with iAMP21 has a known frequency of approximately 2% of B-ALL and is most often identified in older children with ALL and not infants, and the findings of this case series have confirmed these previous findings (Swerdlow et al., 2017).

Four of the nine subtypes of B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities accounted for small fraction of A-ALL (24 cases, 15.0%) and were

reported in a higher number in I-ALL (16.3%) with fewer cases in C-ALL (5.55%). The ALL with "B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged" subtype dominated the B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities subgroup with 16 diagnoses but accounted for under 5% (4.92%) of A-AL, 10.0% of A-ALL, 5.5% of C-ALL, and 10.7% of I-ALL. This finding was consistent but lower than previous reports of *KMT2A* translocations in infant acute leukemia. Previous reports have documented a higher incidence of *KMT2A* translocations in childhood with reports of over approximately 90% of infants less than 12 months of age with these abnormalities and over 120 different translocation partners identified to date. The other infant AL groups with *KMT2A* translocations, A-AML and A-ALAL, did not account for a higher number of diagnoses in the case series. Instead, if included as a group, this aberration accounted for under 5% (4.35%) of the case series, which was a finding in stark contrast to previous studies on the infant population. However, as many *KMT2A* aberrations are cryptic and require specific cytogenomic studies, aberration status may not have been evaluated on all patients in the case series, the diagnoses could overlap with other ICD-O-3/WHO 2017 groups. The diagnosis may have been coded incorrectly but may represent a true difference in the evaluation of less than 12 month population not documented previously as other studies have only included older children and resulted in a higher frequency of *KMT2A* aberrations. The B-lymphoblastic and leukemia/lymphoma with hyperdiploidy subgroup has a known frequency of 25% of childhood leukemia, is uncommon in adults, and is not generally observed in infants. This finding was confirmed in the case series as a single diagnosis was documented, which accounted for 0.30% of A-AL, 0.63% of A-ALL, no cases of C-ALL, and 0.71% of I-ALL (Swerdlow et al., 2017). The single diagnosis of B-lymphoblastic and leukemia/lymphoma with hyperdiploidy in the case series occurred in an older infant aged

greater than or equal to 2 months to less than 12 months, which indicated this rare entity is unlikely to be observed in younger infants with C-ALL. The B-lymphoblastic and leukemia/lymphoma with hyperdiploidy subgroup has been previously reported to account for approximately 5% of ALL in both children and adults, and this finding was confirmed in the case series as it accounted for only six diagnoses or 1.84% of A-AL, 3.77% of A-ALL, no cases in C-ALL, and 4.25% of I-ALL (De Lorenzo et al., 2014). The "B-lymphoblastic and leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*" subgroup has a known frequency of approximately 6% of all B-ALL cases and is relatively common in children and not infants. This finding was confirmed in the case series as a single diagnosis or 0.30% of A-AL, 0.63% of A-ALL, no cases of C-ALL, and 0.71% I-ALL was reported. The single diagnosis of "B-lymphoblastic and leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*" in the case series occurred in an older infant aged 2 months or more to less than 12 months, which indicated this rare entity is unlikely to be observed in younger infants with C-ALL. The final subgroup/subtype T-lymphoblastic leukemia/lymphoma or T-ALL has a known frequency of accounting for approximately 15% of childhood ALL and is more common in adolescence than in younger children. This finding was confirmed by the case series as there were 12 diagnoses, which accounted for 3.69% of A-AL, 7.54% of A-ALL, no cases in C-ALL, and 8.5% of I-ALL (Swerdlow et al., 2017). The exclusivity of T-ALL diagnoses to the I-ALL group indicated this rare entity is unlikely to be observed in younger infants with C-ALL. Although not reported in the SEER registry, approximately 50% to 70% of T-ALL cases have an abnormal cytogenetic finding outside of the ICD-O-3/WHO 2017 subgroup/subtype and may have been further classified if this data were to be deposited in the SEER registry and subsequently observed in the series (Swerdlow et al., 2017).

The diagnostic reporting location findings of ALL were consistent with the known presentation of acute leukemia in infants. They often present urgently to the emergency department or clinic and are generally not a secondary finding via laboratory only testing, but may only be detected after rapid progression and death (Naeim et al., 2018). A-ALL was dominated by diagnoses reported by a hospital inpatient/outpatient or clinic, which accounted for 98.1% of A-ALL, 94.4% of C-ALL, and 98.5% of I-ALL. A mere fraction of cases (0.90%) were reported by a laboratory only, death certificate only, or other hospital outpatient unit or surgery center with one case in each of these groups, respectively; 0.71% of I-ALL accounted for by a laboratory only or death certificate only report, and 5.56% of C-ALL accounted for by other hospital outpatient unit or surgery center reporting.

All cases within the A-ALL subgroup were evaluated for their disease primary site to ensure the diagnoses were consistent with ALL and that they should be included in the cases series. The case series findings were consistent with the known variance across the US in the initial diagnostic workup of acute leukemia recently addressed by CAP and ASH 2017 guidelines (Arber et al., 2017). All 159 cases included in the A-ALL were coded as C42.1-bone marrow, a finding consistent with appropriately diagnosed ALL (Naeim et al., 2018). Following the bone marrow evaluation, subsequent studies used for diagnostic confirmation methodology varied in the A-ALL group but included positive histology; positive histology AND immunophenotyping AND/OR positive genetic studies; positive exfoliative cytology, no positive histology; positive laboratory test/marker study; and unknown methodologies. However, the diagnoses in the case series were dominated by positive histology, which accounted for 116 diagnoses or 35.7% of A-AL, 73.0% of A-ALL, 66.7% of C-ALL, and 73.8% of I-ALL. This finding was consistent with standard workup of leukemia patients using a trephine biopsy

necessary for a diagnosis prior to initiating further reflex studies. The second largest group accounted for only a fraction of the diagnostic confirmation methodologies, and positive histology AND immunophenotyping AND/OR positive genetic studies accounted for 32 diagnoses or 9.84% of A-AL, 20.1% of A-ALL, 16.7% of C-ALL, and 20.5% of I-ALL. This finding was consistent with ASH and CAP guidance regarding the evaluation of leukemia patients necessary for a diagnosis prior to initiating further reflex studies. The final groups that were not recommended, given their inability to provide a fully interpretative result for a query leukemia specimen, accounted for a small number of diagnosis consistent with reports that these methodologies are outdated and no longer meets the standard of care. These groups included positive exfoliative cytology, no positive histology, which accounted for 0.92% of A-AL, 1.89% of A-ALL, 5.56% of C-ALL, and 1.42% of I-ALL. Positive laboratory test/marker study accounted for 1.23% of A-AL, 2.5% of A-ALL, 5.56% of C-ALL, and 2.13% of I-ALL. Unknown diagnostic confirmation methodology accounted for 1.23% of A-AL, 2.5% of A-ALLs, 5.56% of C-ALL, and 2.13% of I-ALL. There were no cases of clinical diagnosis only.

The insurance status findings indicated the majority of ALL cases were insured at diagnosis, primarily with private insurance, otherwise with Medicaid coverage, followed by a small number of patients without insurance or documented insurance status. The insurance status of A-ALL was dominated by insured patients, which accounted for 20.9% of A-AL, 42.7% of the A-ALL, 55.5% of C-ALL, and 41.1% of I-ALL. The insured/no specifics accounted for 3.38% of A-AL, 6.92% of A-ALL, no diagnoses of C-ALL, and 7.81% of the I-ALL. These two groups, insured and insured/no specifics, accounted for 24.3% of A-AL, 49.6% of the A-ALL, 55.5% of C-ALL, and 48.9% of I-ALL. The second largest group, any Medicaid, accounted for 22.4% of A-AL, 45.9% of the A-ALL, 44.4% of C-ALL, and 46.1% of I-ALL. The insurance

status unknown accounted for only 1.23% of A-AL, 2.51% of A-ALL, no cases of C-ALL, and 2.80% of I-ALL. The last group, uninsured accounted for only 0.92% of A-AL, 1.88% of the A-ALL, no cases of C-ALL, and 2.13% of I-ALL.

ALAL. The ALAL group, including all diagnoses less than 12 months in the cases series, composed approximately 4% (3.69%) of all cases in the case series consistent with previous epidemiological studies of infant acute leukemia that indicated ALAL was one of the rarest forms of infant leukemia and is known to account for a small fraction (<5%) of all AL (Brown, 2013; Swerdlow et al., 2017). ALAL diagnosed in those aged 2 months or more to less than 12 months (I-ALAL) dominated in the less than 12 month population with fewer cases in those from birth to less than 2 months (C-ALAL). I-ALAL dominated diagnoses with 83.3% of confirmed cases, and only a small fraction reported in C-ALAL with 16.7%. The I-ALAL cases accounted for 3.08% of all diagnoses within the cases series to a mere 0.62% for C-ALAL, which indicated both groups make up a very small number of diagnoses in the case series. This finding was an anticipated finding as previous studies have indicated that AL diagnoses in children less than 12 months include only a tiny fraction of ALAL diagnoses (Bresters et al., 2002; Brown, 2013).

There was a small range of age at diagnoses in the A-ALAL group. Subdivision across all 12 months in the infant case series included diagnoses limited to a few age groups between birth to less than 12 months of age with little variability within the small range of only few cases (1-2) cases across the series. This finding of more cases of I-ALAL and fewer C-ALAL was confirmed through quantification of the variability in the population represented by a mean age of diagnoses of 5 months (5 months, 18 days of age) with a large standard deviation (5.6 ± 3.7). A-ALAL diagnoses were variable in age and occurred in limited estimated age at diagnose groups between

C-ALAL and I-ALAL. There were distinct trends between C-ALAL and I-ALAL groups for estimated age at diagnosis. A child with C-ALAL between birth to less than 2 months of age is most likely to be diagnosed in the period of birth to less than 1 month, rather than age 1 month or more to less than 2 months of age, a finding similar to the C-AML, but the opposite of the C-ALL group in this case series. This finding may represent the known association of congenital acute leukemia with in utero development or congenital anomalies associated with an increased risk of ALAL development, presenting shortly after birth as confirmed by previous studies using retrospective analysis of Guthrie cards, the known aggressive and ambiguous nature of ALAL that hinder diagnoses or other unidentified risk factors for leukemia development combined with access or proximity to health care professionals in this stage of early life (Brown, 2013; Cao et al., 2016; M. Greaves, 2005; Isaacs, 2003; Rubnitz et al., 2009).

Conversely, a child with ALAL aged 2 months or more to less than 12 months is equally likely to be diagnosed in the period from 4 months or more to less than 8 months of age with fewest diagnoses in the 3 months or more to less than 4 months and 10 months or more to less than 11 months of age groups. Diagnoses across 2 months or more to less than 12 months age group varied very little with a range of one to two diagnoses in each month of age. These findings were consistent with increased incidence of ALAL in pediatric patients aged 1 to 4 years with fewer cases in less than 12 months of age, meaning the number of ALAL diagnoses increase as the age of children increase in the case series (Barrington-Trimis et al., 2017).

The sex of infants in the A-ALAL group included more males (7) versus females (5) diagnosed for a M/F ratio of 1:0.71. Males were more likely to be diagnosed with ALAL as in the A-ALAL less than 12 months of age group as found in 12 infants: 41.7% female versus

58.3% male diagnoses. This finding was the same sex finding as AML, ALL, and the opposite of OAL diagnoses discussed in this chapter.

There were major differences between race and ethnicity groups of A-ALAL, which may represent the race and ethnicity composition of SEER registry areas and the U.S. population, but also has supported differences between acute leukemia lineage. The findings of this case series have showed that non-Hispanic Caucasian infant populations are most likely to be diagnosed with ALAL and are consistent with previous reports that ALAL diagnoses are dominated by Caucasian infants with fewer cases in other races in the U.S. and global populations (Brown, 2013). There were nine diagnoses accounting for 75.0% of A-ALAL diagnoses with the majority diagnosed in non-Hispanic Caucasian (5, 41.7%) followed by Hispanic Caucasian (White; 4, 33.3%) infants. This finding that the majority of diagnoses in Caucasian infants was similar to the findings in the A-AML and A-ALL groups; however, unlike A-ALL and more similar to A-AML, A-ALAL more often occurred in non-Hispanic rather than Hispanic Caucasian (White) infants. Caucasian (White) infants are more likely than non-Hispanic Asian, Pacific Islander, American Indian or Alaska Native infants (3, 25% of A-ALAL), African-American (Black) infants (no cases of A-ALAL), and unknown race (no cases of A-ALAL) infants to be diagnosed with ALAL less than 12 months of age. Diagnoses in Asian or Pacific Islander or American Indian or Alaska Native group infants (3) were a fraction of the number of diagnoses in Caucasian (White) infants (9). These findings indicated the collection of race and ethnicity information can be applied to guide diagnostic testing in infants with a query leukemia presentation.

All 12 cases in the A-ALAL group were placed into the one of four subgroups, which composed a small fraction of (3.69%) of all AL diagnoses in the case series. In the I-ALAL case

series, the cases were more likely to have been categorized using a genetic laboratory study with fewer cases of C-ALAL diagnosed with this methodology. The four subgroups of the ambiguous lineage acute leukemia group were observed in the case series with the majority of cases (4, 1.23%) designated in mixed phenotype acute leukemia, B/myeloid, NOS, accounting for 1.23% of A-AL, 33.3% of the A-ALAL, no cases of C-ALAL, and 33.3 % of the I-ALAL. This finding indicated mixed phenotype acute leukemia, B/myeloid, NOS, is most likely to be diagnosed in an older child aged 2 months or more with fewer cases in younger children less than 2 months of age, and this finding was consistent with the known frequency of the subtype documented previously to account for approximately 1% of acute leukemia, a diagnosis more common in adults than children. The second largest groups, acute undifferentiated leukemia and "mixed phenotype acute leukemia with t(v;11q23); *KMT2A*(MLL) rearranged" subgroups/subtypes accounted for 0.92% of A-AL, 25% of A-ALAL, 8.33% of C-ALAL, and 16.6% of I-ALAL, respectively. These findings were consistent with the known frequency of acute undifferentiated leukemia as a very rare entity without a known precise frequency. "Mixed phenotype acute leukemia with t(v;11q23); *KMT2A*(MLL) rearranged" is similar to AML and ALL with *KMT2A*(MLL) rearrangements that are more common during infancy than in any other age group, but this case series did not support previous reports that this aberration accounted for approximately 90% of all infant leukemia at least when the infant group was limited to those less than 12 months of age (Swerdlow et al., 2017). Even when all *KMT2A*(MLL) classified groups in the case series are combined, this genetic-testing-based stratified group did not account for a majority of acute leukemia diagnoses in the infant population. The smallest group, mixed phenotype acute leukemia, T/myeloid, NOS, accounted for 0.62% of A-AL, 16.6% of A-ALAL, no cases of C-ALAL, and 33.3% of I-ALAL, a finding that was consistent with the unknown

frequency of this rare entity (Swerdlow et al., 2017). These diagnoses of acute undifferentiated leukemia; mixed phenotype acute leukemia, B/myeloid, NOS; and mixed phenotype acute leukemia, T/myeloid, NOS, were based on morphology and/or immunophenotyping data without the need for specific genetic studies to confirm the diagnoses. Genetic studies are not necessary to confirm these diagnoses but may still be performed to confirm a diagnosis given genetic studies for other ALAL groups are exclusive to those leukemia subgroup diagnoses. There were no documented cases of the other genetically defined subgroup in the case series "mixed phenotype acute leukemia with t(9;22)(q34.1;11.2); *BCR-ABL1*." The known frequency of this rare entity is under 1% of all acute leukemia, is more commonly diagnosed in adults than children, and the findings of this dissertation study have supported that it is virtually absent from the infant population.

The diagnostic reporting location findings of ALAL were consistent with the known presentation of acute leukemia in infants, and they often present urgently to the emergency department or clinic and are generally not a secondary finding via laboratory only testing, but may only be detected after rapid progression and death (Naeim et al., 2018). A-ALAL was dominated by diagnoses reported from a hospital inpatient/outpatient or clinic, which accounted for 91.7% of A-ALAL diagnoses, 50% of C-ALAL, and 100.0% of I-ALAL. The remaining cases (8.33%) were reported by a laboratory only in only a single C-ALAL case (50.0%).

All cases within the A-ALAL subgroup were evaluated for their disease primary site to ensure the diagnoses were consistent with ALAL and that they should be included in the case series. All 12 cases included in the A-ALAL were coded as C42.1-bone marrow, a finding that was consistent with appropriately diagnosed ALAL (Naeim et al., 2018). The case series findings were consistent with the known variance in methodologies across the US in the initial diagnostic

workup of acute leukemia, recently addressed by CAP and ASH 2017 guidelines (Arber et al., 2017). Following the bone marrow evaluation, subsequent studies used for diagnostic confirmation methodology varied in the A-ALAL group, but included only positive histology, and positive histology AND immunophenotyping AND/OR positive genetic studies. The positive histology accounted for 10 diagnoses or 3.08% of the cases series, 83.0% of A-ALAL, 50.0% of C-ALAL, and 90.0% of I-ALAL, a finding that was consistent with basic workup of leukemia patients using a trephine biopsy necessary for a diagnosis prior to initiating further reflex studies. The second group, a fraction of the diagnostic confirmation methodologies positive histology AND immunophenotyping AND/OR positive genetic studies, accounted for only two diagnoses or 0.62% of the cases series, 17.0% of A-ALAL, 50.0% of C-ALAL, and 10.0% of I-ALAL, consistent with ASH and CAP guidance regarding the evaluation of leukemia patients necessary for a diagnosis prior to initiating further reflex studies. The final groups, which are not recommended given their inability to provide a fully interpretative result for query leukemia specimen, were not documented in the group positive exfoliative cytology, no positive histology; positive laboratory test/marker study; or clinical diagnosis only, and this finding may indicate that given the rare nature of ALAL all appropriate methodologies were exhausted prior to conclusion of pathology-based laboratory investigations.

The insurance status findings indicated the majority of ALAL cases were insured at diagnosis, primarily with private insurance, followed by a small number of patients with Medicaid coverage, without insurance, or no documented insurance status. The insurance status of the A-ALAL group was dominated by insured patients, which accounted for 2.77% of A-AL, 75.0% of the A-ALAL, 100.0% of C-ALAL, and 30.0% of I-ALAL, with no patients in the subgroup of insured/no specifics. The other groups, any Medicaid, insurance status unknown,

and uninsured accounted for 0.31% of A-AL, 8.33% of the A-ALAL, no cases of C-ALAL, and 10.0% of I-ALAL, respectively.

OAL. The A-OAL group, including all diagnoses less than 12 months in the cases series, composed a small fraction of all cases (2.15%) in the case series consistent with previous epidemiological studies of infant acute leukemia (Brown, 2013). Within the A-OAL group, diagnoses in the younger group of children birth to less than 2 months dominated with fewer cases in the 2 months or more to less than 12 months of age group (C-OAL 71.4% vs. 28.5% for I-OAL). This finding was the inverse of all other lineage stratified groups, meaning AML, ALL, and ALAL were more common in the infant age stratified group with fewer cases in the congenital age stratified group finding in OAL. The C-OAL cases accounted for 1.53% of all diagnoses within the cases series to a mere 0.61% of I-OAL, indicating these groups make up a small number of diagnoses in the infant population.

There were distinct trends between C-OAL and I-OAL groups for estimated age at diagnosis. A-OAL diagnoses are not extremely variable in age and occur in limited estimated age at diagnoses groups between C-OAL and I-OAL. OAL diagnosed in those aged birth to less than 2 months are more common in the less than 12 month population with fewer cases in those 2 months or more to less than 12 months. The age at diagnoses groups were subdivided across all 12 months in the infant case series with diagnoses limited to a few age groups between birth to less than 12 months of age with a small variability of only few cases (1-3) cases across the series. The finding of more cases of C-OAL and fewer cases of I-OAL was confirmed through quantification of the variability in the population represented by a mean age of diagnoses of 1 month (1 month, 3 days of age) with only a small standard deviation (1.1 ± 1.5). There were no diagnoses in the 3 months or more to less than 4 months and 5 months or more to less than 11

month age groups. A child with C-OAL between birth to less than 2 months of age is slightly more likely to be diagnosed in the period of birth to less than 1 month, rather than aged 1 months or more to less than 2 months of age, similar to the findings in C-AML and C-ALAL, but the opposite finding of the C-ALL group. This finding may represent the known association of congenital acute leukemia with in utero development or congenital acquired anomalies or environmental risk factors for leukemia development in conjunction with access or proximity to health care professionals in this stage of life; however, as this category is used for leukemia diagnoses that lack the features of other subgroups, the documentation of more cases early in life was consistent with the limited stratification available for an emergent ambiguous presentation in a young infant (Brown, 2013; Cao et al., 2016; Isaacs, 2003). Conversely, a child with OAL between 2 months or more to less than 12 months is most likely to be diagnosed in the period from 4 months or more to less than 5 months of age with no diagnoses in older age groups in the case series. Diagnoses across 2 months or more to less than 12 months age group varied little between the range of only a single diagnosis in each month of age group. This finding was consistent with lack of appropriate classification of acute leukemia in the congenital groups unlike the stratification available for those 2 months or more to less than 12 months of age infant group, and previous reports of infant leukemia diagnoses were more likely to be classified using morphology, immunophenotyping, and cytogenetics unlike the disease in younger infants with congenital leukemia (Barrington-Trimis et al., 2017).

The sex of infants in the A-OAL group included more females (4) versus males (3) diagnosed for a M/F ratio of 0.75:1. Females are more likely to be diagnosed with OAL in the A-OAL less than 12 months of age group as found in 7 infants: 57.1% female versus 42.9% male

diagnoses. This finding was the opposite of AML, ALL, and ALAL diagnoses discussed in this chapter.

There were major differences between race and ethnicity groups of A-OAL, which may represent the race and ethnicity composition of SEER registry areas and the U.S. population, but also has supported differences between acute leukemia types. The findings of this case series showed that Hispanic Caucasian infant populations were most likely to be diagnosed with ALAL and were consistent with previous reports that suggested ALAL diagnoses are dominated by Caucasian infants with fewer cases in other races in the U.S. and global populations (Brown, 2013). The A-OAL diagnoses stratified by race and ethnicity indicated the majority of OAL diagnoses occurred in Caucasian (White) infant race group: the highest in Hispanic ethnicity, followed by non-Hispanic Caucasian (White) infants. The majority of OAL diagnoses occurred in Caucasian (White) infants with five diagnoses that accounted for 71.4% of A-OAL diagnoses with the majority diagnosed in Hispanic Caucasian (3, 42.8%), followed by non-Hispanic Caucasian (White; 2, 28.6%) infants. This finding that the majority of diagnoses occurred in Caucasian infants was similar to the findings in the A-AML, A-ALL, and A-ALAL groups; however, like A-ALL and less similar to the ethnicity findings in A-AML and A-ALAL, A-OAL more often occurred in Hispanic rather than non-Hispanic Caucasian (White) infants. The remaining two cases were documented in the combined Asian or Pacific Islander and African-American (Black) non-Hispanic infant group (1, 14.3%). This finding indicated Caucasian (White) infants are more likely than Hispanic and non-Hispanic African-American (Black; 1, 14.3% of A-OAL), Asian or Pacific Islander (1, 14.3% of A-OAL), American Indian or Alaska Native (no cases of A-OAL) infants to be diagnosed with OAL under less than 12 months of age. Diagnoses in the African-American (Black, 1) and Asian or Pacific Islander infant groups (1)

were only slightly lower than the number of diagnoses in Caucasian (White) infants (5). These findings indicated the collection of race and ethnicity information can be applied to guide diagnostic testing in infants with a query leukemia presentation.

The A-OAL cases were placed into designated ICD-O-3/WHO 2017 aligned leukemia group acute myeloid leukemia and related neoplasms and placed into a single subgroup acute leukemia, NOS, which composed a small fraction of (2.15%) of all acute leukemia diagnoses in the case series. This finding was consistent with the known frequency of O-AL, a finding used only in the absence of other group specific findings in this case series and the WHO 2017.

The diagnostic reporting location findings of A-OAL were consistent with the known presentation of acute leukemia in infants, and they often present urgently to the emergency department or clinic and are generally not a secondary finding via laboratory only testing, but may only be detected after rapid progression and death (Naeim et al., 2018). The A-OAL group was dominated by diagnoses reported by a hospital inpatient/outpatient or clinic, which accounted for 71.4% of A-OAL, 80.0% of C-OAL, and 50.0% of I-OAL. However, unlike other leukemia groups, the remaining A-OAL cases (28.6%) were reported by autopsy only or physician's office/private medical practitioner (LMD) in only a single C-OAL case (20.0% of C-OAL) and single I-OAL case (50.0% of I-OAL). This finding that the majority of A-OAL cases were not diagnosed until after death was consistent with the limited information available to classify these diagnoses, which may have inhibited appropriate recognition of the disease and treatment administration prior to death (Naeim et al., 2018).

All cases within the A-OAL subgroup were evaluated for their disease primary site to ensure the diagnoses were consistent with OAL and that they should be included in the cases series. All seven cases included in the A-OAL were coded as C42.1-bone marrow, a finding

consistent with appropriately diagnosed OAL (Naeim et al., 2018). The case series diagnostic confirmation methodology varied in the A-OAL group, which was consistent with the known variance in methodologies across the US in the initial diagnostic workup of acute leukemia, recently addressed by CAP and ASH 2017 guidelines (Arber et al., 2017). Following the bone marrow evaluation, subsequent studies used for diagnostic confirmation methodology included only positive histology, positive laboratory test/marker study, and unknown. The diagnoses were dominated by positive histology, which accounted for four diagnoses or 1.23% of A-AL, 57.1% of A-OAL, 40.0% of C-OAL, and 100.0% of I-OAL. This finding was consistent with standard workup of leukemia patients using a trephine biopsy necessary for a diagnosis prior to initiating further reflex studies. The second group, accounting for only a fraction of the diagnostic confirmation methodologies, unknown, accounted for only two diagnoses or 0.62% of A-AL, 28.6% of A-OAL, 40.0% of C-OAL, and no cases of I-ALAL. The final group, positive laboratory test/marker study, accounted for a single diagnosis or 0.31% of the case series, 14.3% of A-OAL, 20.0% of C-OAL, and no cases of I-OAL. The remaining groups were not documented in the case series positive histology AND immunophenotyping AND/OR positive genetic studies; positive exfoliative cytology, no positive histology; positive laboratory test/marker study; or clinical diagnosis only.

The insurance status findings indicated the majority of OAL cases had an unknown insurance status, followed by a small number of patients with Medicaid coverage, or no documented insurance status. The insurance status of the A-OAL group was dominated by insurance status unknown, which accounted for 1.23% of diagnoses in the case series: 57.1% of the A-OAL, 60.0% of C-OAL, and 50.0% of I-OAL with no patients in the subgroup of insured or uninsured. The other group, any Medicaid, accounted for 0.62% of OAL diagnoses in the case

series, 28.6% of the A-OAL, 20.0% of C-OAL, and 50.0% of I-OAL. Only a single diagnosis in the insured/no specifics group accounted for 14.3% of OAL diagnoses in the case series, 20.0% of the C-OAL, and no cases of I-OAL. These findings were unique to OAL and differed significantly from AML, ALL, and ALAL patients in the case series but may be reflective of the hasty nature of these diagnosis that often occur only after the demise of the infant.

Research Question 2.1. Congenital acute leukemia diagnoses accounted for approximately one fifth of diagnoses in the case series (59, 18.1%). The proportion of congenital leukemia diagnoses in 1- to 2-month-old infants in the leukemia subtype stratified groups differed significantly in the birth to less than 2 months of age group with the most likely diagnosis of C-AML and the least likely C-ALAL. The C-AL were divided into two groups either from birth to less than 1 (C-leukemia^{B-1}) or 1 month or more to less than 2 months (C-leukemia$^{1-2}$). The largest group, C-AML, included 34 diagnoses and accounted for 57.7% of all C-AL in the case series. C-ALL included 18 diagnoses and accounted for 31.0% of all C-AL. C-OAL included five diagnoses and accounted for 8.47% of C-AL. C-ALAL included a mere two diagnoses and accounted for 3.38% of C-AL in the case series.

The evaluation of the association between age of diagnoses and the lineage of C-AL using the chi-square test ($\alpha = 0.05$), $X^2 = 4.676$, and $p = .197$ indicated there was no age preference for AL lineage in the C-AL group. The association test findings indicated there was no statistically significant relationship between age at diagnoses in either C-AL^{B-1} or C-AL$^{1-2}$ and C-AL lineage C-AML, C-ALL, C-ALAL, or C-OAL. Infants aged birth to less than 2 months were equally likely to be diagnosed in both C-AL^{B-1} and C-AL$^{1-2}$ groups within C-AML, C-ALL, C-ALAL, or C-OAL.

The majority of C-AL diagnoses occurred in the birth less than 1 month age group (37, 11.7%) with the remainder in the 1 month or more to less than 2 months (23, 6.4%) of age group. C-AML is most likely to be diagnosed in children from birth to less than 1 month with fewer cases in the greater than or equal to 1 month to less than 2 months of age group. In the age-specific groups, C-AML $^{B-1}$ included 24 diagnoses and accounted for 40.6% of C-AL, 70.6% of C-AML, 7.38% of A-AL, and 63.1% of C-AL in the birth to less than 1 month group. C-AML$^{1-2}$ included 10 diagnoses and accounted for 16.9% of C-AL, 29.4% of C-AML, 3.07% of A-AL, and 47.6% of C-AL in the 1 month or more to less than 2 months group. C-ALL is most likely to be diagnosed in children from 1 month or more to less than 2 months of age with fewer cases in the birth to less than 1 month of age group. C-ALL $^{B-1}$ included eight diagnoses and accounted for 13.6% of C-AL, 44.4% of C-ALL, and 21.1% of C-AL in the birth to less than 1 month group. C-ALL$^{1-2}$ included 10 diagnoses and accounted for 16.9% of C-AL, 55.6% of C-ALL, 3.07% of AL, and 47.6% of C-AL in the 1 month or more to less than 2 months group. C-OAL is most likely to be diagnosed in children from birth to less than 1 month with fewer cases in the 1 month or more less than 2 months of age. C-OAL $^{B-1}$ included four diagnoses and accounted for 6.77% of C-AL, 80.0% of C-OAL, 1.23% of A-AL, and 10.5% of C-AL in the birth to less than 1 month group. C-OAL$^{1-2}$ included a single diagnosis and accounted for 1.69% of C-AL, 20.0% of C-OAL, 0.31% of A-AL, and 4.76% of C-AL in the 1 month or more to less than 2 months group. All C-ALAL diagnoses occurred in the birth less than 1 month group as there were no diagnoses of C-ALAL in the 1 month or more to less than 2 months group. C-ALAL $^{B-1}$ included two diagnoses and accounted for 3.39% of C-AL, 100.0% of C-ALAL, 0.61% of A-AL, and 5.26% of C-AL in the birth to less than 1 month group.

Research Question 2.2. Infant acute leukemia diagnoses accounted for four fifths of diagnoses in the case series (265, 81.5%). The largest group, I-ALL, included 141 diagnoses and accounted for 43.4%% of I-AL in the case series. I-AML included 113 diagnoses and accounted for 34.8% of I-AL. I-ALAL included 10 diagnoses and accounted for 3.08% of I-AL, and I-OAL included a mere two diagnoses and accounted for 0.62% of A-AL. The proportion of infant leukemia diagnoses in the 2 months or more to less than 12 months leukemia lineage stratified groups differed significantly across the case series with the most likely diagnosis of I-AML in children aged 11 months or more to less than 12 months with 21 diagnoses, and the least likely was I-OAL, given it was not documented in most age groups in the series.

The evaluation of the association between age of diagnoses and the leukemia lineage of I-AL within the subgroup using the chi-square test ($\alpha = 0.05$), $X^2 = 26.28$, and $p = .503$ indicated there was no age preference for AL leukemia lineage in the I-AL group. The findings indicated there was no statistically significant relationship between age at diagnoses in either I-AL$^{2-3}$, I-AL$^{3-4}$, I-AL$^{4-5}$, I-AL$^{5-6}$, I-AL$^{6-7}$, I-AL$^{7-8}$, I-AL$^{8-9}$, I-AL$^{9-10}$, I-AL$^{10-11}$, or I-AL$^{11-12}$ and I-AL leukemia lineage, I-AML, I-ALL, I-ALAL, or I-OAL. Infants aged 2 months or more to less than 12 months are equally likely to be diagnosed in all I-AL$^{2-<12}$ age groups with AML, ALL, ALAL, or I-OAL.

I-ALL was the most observed leukemia type in the 2 months or more to less than 3 months age group (18). In the age specific groups, I-ALL$^{2-3}$ included 13 diagnoses and accounted for 4.88% of I-AL, 9.22% of I-ALL, 72.2% of AL$^{2-3}$, and 4.00% of A-AL. I-AML$^{2-3}$ included four diagnoses and accounted for 1.50% of I-AL, 3.54% of I-AML, 0.22% of I-AL$^{2-3}$, and 1.23% of A-AL. I-OAL$^{2-3}$ included one diagnosis and accounted for 0.31% of I-AL, 50.0% of I-OAL,

5.56% of I-AL[2-3], and 0.30% of A-AL. There were no diagnoses of I-ALAL in the 2 months or more to less than 3 months group.

I-ALL was the most observed leukemia type in in the 3 months or more to less than 4 months age group (16). I-ALL[3-4] included 11 diagnoses and accounted for 4.14% of I-AL, 7.80% of I-ALL, 68.8% of I-AL[2-3], and 3.38% of A-AL. I-AML[3-4] included four diagnoses and accounted for 3.54% of I-AL, 1.50% of I-AML, 25.0% of I-AL[3-4], and 1.23% of A-AL. I-ALAL[3-4] included one diagnosis and accounted for 0.31% of I-AL, 100.0% of I-ALAL, 6.25% of I-AL[3-4], and 0.30% of A-AL. There were no diagnoses of I-OAL in the 3 months or more to less than 4 months group.

I-AML was the most observed leukemia type in in the 4 months or more to less than 5 months age group (25). I-ALL[4-5] included 10 diagnoses and accounted for 3.76% of I-AL, 7.09% of I-ALL, 40.0% of I-AL[4-5], and 3.07% of A-AL. I-AML[4-5] included 12 diagnoses and accounted for 4.51% of I-AL, 10.6% of I-AML, 48.0% of I-AL[4-5], and 3.69% of A-AL. I-ALAL[4-5] included two diagnoses and accounted for 0.75% of I-AL, 20.0% of I-ALAL, 8.00% of I-AL[4-5], and 0.62% of A-AL. I-OAL[4-5] included one diagnosis and accounted for 0.31% of I-AL, 50.0% of I-ALAL, 4.00% of I-AL[4-5], and 0.30% of A-AL.

I-ALL was the most observed leukemia type in in the 5 months or more to less than 6 months age group (25). I-ALL[5-6] included 12 diagnoses and accounted for 4.51% of I-AL, 8.51% of I-ALL, 48.0% of I-AL[5-6], and 3.69% of A-AL. I-AML[5-6] included 11 diagnoses and accounted for 4.14% of I-AL, 9.73% of I-AML, 44.0% of I-AL[5-6], and 3.38% of A-AL. I-ALAL[5-6] included two diagnoses and accounted for 0.75% of I-AL, 20.0% of I-ALAL, 8.0% of I-AL[5-6], and 0.62% of A-AL. There were no diagnoses of I-OAL in the 5 months or more to less than 6 months group.

I-ALL was the most observed leukemia type in in the 6 months or more to less than 7 months age group (24). I-ALL$^{6-7}$ included 14 diagnoses and accounted for 5.26% of I-AL, 9.92% of I-ALL, 58.3% of I-AL$^{6-7}$, and 4.30% of A-AL. I-AML$^{6-7}$ included 10 diagnoses and accounted for 3.76% of I-AL, 8.8% of I-AML, 41.7% of I-AL$^{6-7}$, and 3.07% of A-AL. There were no diagnoses of I-ALAL and I-OAL in the 6 months or more to less than 7 months age group.

I-ALL was the most observed leukemia type in in the 7 months or more to less than 8 months age group (34). I-ALL$^{7-8}$ included 20 diagnoses and accounted for 7.52% of I-AL, 14.1% of I-ALL, 58.8% of I-AL$^{7-8}$, and 6.15% of A-AL. I-AML$^{7-8}$ included 12 diagnoses and accounted for 4.51% of I-AL, 10.6% of I-AML, 35.3% of I-AL$^{7-8}$, and 3.69% of A-AL. I-ALAL$^{7-8}$ included two diagnoses and accounted for 0.75% of I-AL, 20.0% of I-ALAL, 5.88% of I-AL$^{7-8}$, and 0.62% of A-AL. There were no diagnoses of I-OAL in the 7 months or more to less than 8 months age group.

I-AML was the most observed leukemia type in in the 8 months or more to less than 9 months age group (27). I-ALL$^{8-9}$ included 12 diagnoses and accounted for 4.51% of I-AL, 8.51% of I-ALL, 44.4% of I-AL$^{7-8}$, and 3.69% of A-AL. I-AML$^{8-9}$ included 15 diagnoses and accounted for 5.63% of I-AL, 13.3% of I-AML, 55.6% of I-AL$^{7-8}$, and 4.62% of A-AL. There were no diagnoses of I-ALAL and I-OAL in the 7 months or more to less than 8 months age group.

I-AML and I-ALL were the equally observed leukemia type in in the 9 months or more to less than 10 months age group (28). I-ALL$^{9-10}$ included 14 diagnoses and accounted for 5.26% of I-AL, 12.4% of I-ALL, 50.0% of I-AL$^{9-10}$, and 4.30% of A-AL. I-AML$^{9-10}$ included 14 diagnoses and accounted for 5.26% of I-AL, 9.92% of I-AML, 50.0% of I-AL$^{9-10}$, and 4.30% of A-AL. There were no diagnoses of I-ALAL and I-OAL in the 9 months or more to less than 10 months age group.

I-ALL was the most observed leukemia type in in the 10 months or more to less than 11 months age group (28). I-ALL$^{10\text{-}11}$ included 17 diagnoses and accounted for 6.39% of I-AL, 12.1% of I-ALL, 60.7% of I-AL$^{10\text{-}11}$, and 5.23% of A-AL. I-AML$^{10\text{-}11}$ included 10 diagnoses and accounted for 3.76% of I-AL, 8.85% of I-AML, 35.7% of I-AL$^{10\text{-}11}$, and 3.07% of A-AL. I-ALAL$^{10\text{-}11}$ included one diagnosis and accounted for 0.31% of I-AL, 10.0% of I-ALAL, 3.58% of I-AL$^{10\text{-}11}$, and 0.30% of A-AL. There were no diagnoses of I-OAL in the 10 months or more to less than 11 months age group.

I-AML was the most observed leukemia type in in the greater than or equal to 11 to less than 12 months age group (41). I-ALL$^{11\text{-}12}$ included 18 diagnoses and accounted for 6.76% of I-AL, 12.8% of I-ALL, 42.9% of I-AL$^{11\text{-}12}$, and 5.54% of A-AL. I-AML$^{11\text{-}12}$ included 21 diagnoses and accounted for 7.89% of I-AL, 18.6% of I-AML, 51.2% of I-AL$^{11\text{-}12}$, and 6.46% of A-AL. I-ALAL$^{11\text{-}12}$ included two diagnoses and accounted for 0.75% of I-AL, 20.0% of I-ALAL, 4.88% of I-AL$^{11\text{-}12}$, and 0.62% of A-AL. There were no diagnoses of I-OAL in the 11 months or more to less than 12 months age group.

Research Question 2.3. More males than females were diagnosed with acute leukemia in the case series; however, the proportion of infant female and male leukemia diagnoses in leukemia lineage stratified groups differed significantly between groups. Males accounted for 55.4% and females 44.6% of the infant diagnoses in the case series.

The evaluation of the association between sex and the AL lineage using the chi-square test ($\alpha = 0.05$), $X^2 = 5.17$, and $p = .639$ indicated there were no sex preference for AL lineage in the case series. The findings indicated there was no statistically significant relationship between sex and development of AL type, meaning females and males are equally likely to be diagnosed

in all AL groups: C-AML, C-ALL, C-ALAL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, or I-OAL.

Overall, more males than females were diagnosed with acute leukemia in the case series; however, males dominated the diagnoses in only three groups, including I-AML, I-ALL, and I-ALAL, which as a collective unit accounted for 85.0% of AL^M diagnoses. Females dominated the diagnoses in only two groups, including C-ALL and C-OAL. These two combined accounted for 10.4% of AL^F diagnoses. The remaining three groups, C-AML, C-ALAL, and I-OAL, included an equal number of female and male diagnoses and combined accounted for 9.44% of AL^M and 13.3% of AL^F diagnoses. The largest group, I-ALL^M, included 86 diagnoses and accounted for 61.0% of all I-ALL, 47.7% of all acute leukemia males (I-AL^M), and 26.5% of A-AL with the remaining 55 diagnoses designated I-ALL^F that accounted for 39.0% of I-ALL, 37.9 % of I-AL^F, and 16.0% of A-AL. These findings indicated more males than females were diagnosed with I-ALL in the case series. I-AML^M included 61 diagnoses and accounted for 54.0% of I-AML, 33.9 % of I-AL^M, and 18.8% of I-AL, and the remaining 52 diagnoses, designated I-AML^F, accounted for 46.0% of I-AML, 35.9 % of A-AL^F, and 16.0% of A-AL. These findings indicated more males than females were diagnosed with I-AML in the case series. C-AML^M and C-AML^F included 17 diagnoses and both accounted for 50.0% of C-AML, 5.23% of I-AL, 9.44% of A-AL^M, and 11.7 % of A-AL^F, respectively. These findings indicated males and females were equally diagnosed with C-AML in the case series. C-ALL^F included 12 diagnoses and accounted for 66.7% of C-ALL, 8.28 % of A-AL^F, and 3.69% of A-AL, and the remaining six diagnoses, designated C-ALL^M, accounted for 33.3% of C-ALL, 3.33 % of A-AL^M, and 1.85% of A-AL. These findings indicated more females than males were diagnosed with C-ALL in the case series. I-$ALAL^M$ included six diagnoses and accounted for 60.0% of I-

ALAL, 3.3 % of A-AL^{M}, and 1.85% of A-AL, and the remaining four diagnoses, designated I-ALAL^{F}, accounted for 40.0% of C-ALL, 2.76 % of A-AL^{F}, and 1.23% of A-AL. These findings indicated more males than females were diagnosed with I-ALAL in the case series. C-OAL^{F} included three diagnoses and accounted for 60.0% of C-OAL, 2.07% of A-AL^{F}, and 0.92% of A-AL, and the remaining two diagnoses, designated C-OAL^{M}, accounted for 40.0% of C-OAL, 1.11% of A-AL^{M}, and 0.62% of A-AL. These findings indicated more females than males were diagnosed with C-OAL in the case series. C-ALAL^{M} and C-ALAL^{F} included one diagnosis and accounted for 50.0% of C-ALAL and 0.30% of A-AL and accounted for 0.55% of A-AL^{M} and 0.69% of A-AL^{F}, respectively. These findings indicated males and females were equally diagnosed with C-ALAL in the case series. I-OAL^{M} and I-OAL^{F} included one diagnosis and accounted for 50.0% of C-ALAL, 0.30% of A-AL with 0.55% of A-AL^{M}, and 0.69% of A-AL^{F}, respectively. These findings indicated males and females were equally diagnosed with I-OAL in the case series.

Research Question 2.4. All registries in the SEER 18 group were documented in the case series with diagnoses of I-AML and I-ALL documented in all registry areas reported; however, C-AML, C-ALL, and I-ALAL were limited in the reported registry areas. I-AML and I-ALL were not limited in geospatial distribution across the US as they were documented in all registries. Comparatively, C-AML, C-ALL, C-ALAL, C-OAL, I-ALAL, and I-OAL were limited in their geospatial distribution across the US in this case series. C-AML, C-ALL, and I-ALAL were diagnosed in 64.7%, 53.0%, and 41.4% of registries, respectively. C-ALAL, C-OAL, and I-OAL were diagnosed in 11.8%, 23.5%, and 11.8% of registries, respectively.

Although limited in geospatial distribution across the US in this case series, the largest number of C-AML diagnoses were reported in California (excluding SF/SJM/LA [10]), the

fewest (1) in Connecticut, Greater Georgia, and New Mexico, respectively. Diagnoses for C-AML occurred in three of four U.S. regions as divided by the United States Census Bureau, including Northeast, South, and West; there were no diagnoses reported in a registry located in the Midwest region; however, as there is only one registry (Iowa) representing this entire region, it was difficult to conclude there was a reduced incidence of C-AML is this U.S. region. The two largest groups, West and Northwest, included 21 and 10 diagnoses, respectively with the smallest group the South that accounted for only three of the 34 C-AML diagnoses.

Although limited in geospatial distribution across the US in this case series, the largest number of C-ALL diagnoses were reported in California (excluding SF/SJM/LA [6]), the fewest (1) in Atlanta (Metropolitan), Connecticut, Detroit (Metropolitan), Greater Georgia, New Jersey, and San Francisco-Oakland SMSA, respectively. Diagnoses for C-ALL occurred in three of four U.S. regions as divided by the United States Census Bureau: Northeast, South, and West; there were no diagnoses reported in a registry located in the Midwest region; however, as there was only one registry (Iowa) representing this entire region, it was difficult to conclude there was a reduced incidence of C-ALL is this U.S. region. The two largest groups, West and Northwest, included 13 and three diagnoses, respectively with the smallest group being the South, which accounted for only two of the 18 C-ALL diagnoses.

Limited in geospatial distribution across the US in this case series, the diagnoses for C-ALAL occurred in only two of four U.S. regions as divided by the United States Census Bureau: South and West; there were no diagnoses reported in a registry located in the Midwest region; however, as there was only one registry (Iowa) representing this entire region, it was difficult to conclude there was a reduced incidence of C-ALAL is this U.S. region. However, there were numerous registries covering the Northeast region, but no C-ALAL diagnoses were reported. As

there were only two diagnoses of C-ALAL in the South and West, each included only one diagnosis. The limited distribution across the US in this case series is consistent with the rare nature of the C-ALAL group, which accounted for a mere 0.60% of A-AL.

Limited in geospatial distribution across the US in this case series the diagnoses for C-OAL occurred in two of four U.S. regions as divided by the United States Census Bureau: South and West. There were no diagnoses reported in a registry located in the Midwest region; however, as there was only one registry (Iowa) representing this entire region, it was difficult to conclude there was a reduced incidence of C-OAL is this U.S. region. However, there were numerous registries covering the Northeast region, but no C-OAL diagnoses were reported. The largest group, the West, included three diagnoses with the smallest group, the South, which accounted for only two of the five C-OAL diagnoses. The limited distribution across the US in this case series was consistent with the rare nature of the C-OAL group, which accounted for a mere 1.5% of A-AL.

The diagnoses of I-AML were well distributed across the SEER registries in this case series. The largest number of I-AML diagnoses were reported in California (excluding SF/SJM/LA [25]), and the fewest (1) were in the Alaska Natives registry. Diagnoses for I-AML occurred in all four U.S. regions as divided by the United States Census Bureau: Northeast, Midwest, South, and West. The two largest groups, the West and South, included 75 and 21 diagnoses, respectively, followed by 14 and 3 diagnoses in the Northeast and Midwest regions, respectively, of the 113 I-AML diagnoses.

The diagnoses of I-ALL were well distributed across the SEER registries in this case series. The largest number of I-ALL diagnoses were reported in California (excluding SF/SJM/LA [39]), and the fewest (1) were in the Alaska Natives, Connecticut, and Hawaii

registries, respectively. Diagnoses for I-ALL occurred in all four U.S. regions as divided by the United States Census Bureau: Northeast, Midwest, South, and West. The two largest groups, West and South, included 93 and 30 diagnoses, respectively, followed by 16 and 2 diagnoses in the Northeast and Midwest regions, respectively, of the 141 I-ALL diagnoses.

Limited in geospatial distribution across the US in this case series, the diagnoses for I-ALAL occurred in three of four U.S. regions as divided by the United States Census Bureau: Northeast, South, and West; there were no diagnoses reported in a registry located in the Midwest region; however, as there was only one registry (Iowa) representing this entire region, it was difficult to conclude there was a reduced incidence of C-ALAL is this U.S. region. The largest number of I-ALAL diagnoses (2) were reported in Greater Georgia, San Francisco-Oakland SMSA, and Utah, respectively with the fewest (1) in the California (excluding SF/SJM/LA), Hawaii, Los Angeles, and New Jersey registries, respectively. This limited distribution across the US for I-ALAL was consistent with the rare nature of the leukemia group, which accounted for only 3.1% of A-AL.

Limited in geospatial distribution across the US in this case series the diagnoses for I-OAL occurred in only one of four U.S. regions as divided by the United States Census Bureau: the West; there were no diagnoses reported in a registry located in the Midwest region; however, as there was only one registry (Iowa) representing this entire region, it was difficult to conclude there was a reduced incidence of I-OAL is this U.S. region. However, there were numerous registries covering the Northeastern and Southern regions, but no I-OAL diagnoses were reported. The West included a mere two diagnoses, accounting for all I-OAL. The limited distribution across the US in this case series is consistent with the rare nature of the leukemia group, which accounted for a mere 0.60% of A-AL in the case series.

Research Question 2.5. The top 20% highest proportion registry region counties included California (excluding SF/SJM/LA), Greater Georgia, Los Angeles, and New Jersey, which occurred in three of four U.S. regions as divided by the United States Census Bureau: Northeast, West, and South. The highest proportion registry regions accounted for 53.9% of A-AL. In the highest proportion SEER registry areas with the highest number of infant AL diagnoses in the families below poverty (100%) group, and findings were not similar across geospatial areas in the case series. The families below poverty (100%) group was highest in the Greater Georgia (13.9%, 13.9% ± 5.3) registry area with Los Angeles (13.6%, 13.6%; with data collected from one county) and California (excluding SF/SJM/LA; 11.9%, 12.16%, ± 4.7) reporting similar families below poverty. Comparatively, the families below poverty (100%) group was significantly less in the New Jersey (7.1%, 5.4% ± 3.8) registry region. These findings indicated families below poverty levels differ in areas with the most acute leukemia diagnoses and were unlikely to have affected the diagnoses of acute leukemia in this case series.

In the highest proportion SEER registry areas with the highest number of infant AL diagnoses, the persons below poverty (100%) group differed significantly across geospatial areas in the case series. The persons below poverty (100%) group was highest in in the Greater Georgia (18.54%, 18.82% ± 7.8) registry area with Los Angeles (17.12%, 17.12%; with data collected from one county), and California (excluding SF/SJM/LA; 16.03%, 16.03% ± 5.0) reporting similar persons below poverty. Comparatively, the persons below poverty (100%) group was a slightly less in in the New Jersey (9.37%, 8.01% ± 4.25) registry region. These findings indicated persons below poverty levels differ in areas with the most acute leukemia diagnoses and were unlikely to have affected the diagnoses of acute leukemia in this case series.

In the highest proportion SEER registry areas with the highest number of infant AL diagnoses, the % unemployed group, differed significantly across geospatial areas in the case series. The % unemployed group was highest in California (excluding San Francisco/San Jose-Monterey/Los Angeles; 12.0%, 12.3%, ± 2.51) registry area with Los Angeles (10.8%, 10.8%; with data collected from one county) reporting a slightly lower percent unemployed, followed by Greater Georgia (9.7%, 9.5% ± 2.3). The lowest, 33% less than the region with the highest % unemployed (California, excluding SF/SJM/LA) was reported in New Jersey (9.37%, 8.01% ± 4.25). These findings indicated unemployment levels differ in areas with the most acute leukemia diagnoses and were unlikely to have affected the diagnoses of acute leukemia in this case series.

In the highest proportion SEER registry areas with the highest number of infant AL diagnoses, median family income ($/year), differ significantly across geospatial areas in the case series. The median family income ($/year) was highest in the New Jersey ($90,587 ± 17,986) registry area with California (excluding SF/SJM/LA; $66,820 ± 13,537) and Los Angeles ($62,630; with data collected from one county) reporting similar median family income ($/year). The lowest median family income ($/year) of 36.4% was less than the region with the highest (New Jersey) and was reported in Greater Georgia ($57,556 ± 14,779). These findings indicated median family income levels differ in areas with the most acute leukemia diagnoses and were unlikely to have affected the diagnoses of acute leukemia in this case series.

In the highest proportion SEER registry areas with the highest number of infant AL diagnoses, number of foreign-born individuals ($N \pm SD$), differed significantly across geospatial areas in the case series. The number of foreign-born individuals ($N \pm SD$) was highest in the New Jersey (22,123 ± 10,646) registry area, followed by California (excluding SF/SJM/LA; 19,690 ±

5,575), Greater Georgia (5,813 ± 4,068) and Los Angeles (3,530; with data collected from one county). Immigrants were estimated to comprise 13% of the U.S. population, and represented a proportion of the 2010 census, and each SEER region immigrant population differed across geospatial areas in the case series (Grieco, Acosta, & de la Cruz, 2012; Montealegre, Zhou, Amirian, & Scheurer, 2014). The number of foreign-born individuals for California (excluding SF/SJM/LA; 19,690 ± 5,575) and Los Angeles (3,530; with data collected from one county) combined represented 0.06 ± 0.77% (23,220 ± 5,575) of the California population (37,253,956). The number of foreign-born individuals for New Jersey (22,123 ± 10,646) represented 0.25 ± 0.37% of the New Jersey population (8,791,894). The number of foreign-born individuals for Greater Georgia (5,813 ± 4,068) represented 0.06 ± 0.10% of the Georgia population (9,687,653). These findings indicated the number of foreign born individual levels differ in areas with the most acute leukemia diagnoses and were unlikely to have affected the diagnoses of acute leukemia in this case series.

Research Question 2.6. More children were alive following diagnosis with acute leukemia than dead in the case series with a small portion with an unknown posttreatment status; however, the differences in leukemia lineage age stratified groups were significant between groups. The diagnoses of infants with C-AML, C-ALL, I-AML, and I-ALL in this case series were most likely to be alive rather than deceased. Comparatively, the diagnoses of infants with C-ALAL in this case series were equally likely to be alive versus deceased, and C-OAL were most likely to be dead rather than alive.

The evaluation of the association between vital status and the type of AL using the chi-square test ($\alpha = 0.05$), $X^2 = 9.91$, $p = .194$ indicated there was no vital status preference (alive or dead) for AL lineage age group in the case series. The findings indicated there was no

statistically significant relationship between vital status and AL lineage age group, meaning infants are equally likely to be deceased following treatment in all AL groups: C-AML, C-ALL, C-ALAL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, or I-OAL.

The largest number of infants with C-AML diagnoses were alive (82.5%) after diagnosis with the remaining dead (17.6%), but nearly one fifth of infants diagnosed with C-AML in the case series were dead following treatment with the death attributable to this cancer diagnosis. Death from C-AML accounted for 17.6% of C-AML, 10.2% of C-AL, and 1.85% of A-AL. Alive status from C-AML accounted for 82.4% of C-AML, 47.4% of C-AL, and 8.65% of A-AL. These findings indicated infants diagnosed with C-AML in this case series were most likely to be alive rather than deceased, and those surviving accounted for a mere 1.85% of A-AL, but deaths from C-AML accounted for approximately 10% of A-AL deaths.

Approximately one half of infants diagnosed with C-ALL in the case series were dead following treatment with the death attributable to this cancer diagnosis. The largest number of C-ALL diagnoses were alive (55.6%) with fewer cases dead (44.4%) following diagnosis. Death from C-ALL accounted for 44.4% of C-ALL, 10.2% of C-AL, and 1.85% of A-AL. Alive status from C-ALL accounted for 55.6% of C-ALL, 13.5% of C-AL, and 2.46% of A-AL. These findings indicated infants diagnosed with C-ALL in this case series were most likely to be alive rather than deceased. Those surviving accounted for a mere 1.85% of A-AL, and deaths from C-ALL accounted for approximately 2.5% of A-AL.

Approximately one half of infants diagnosed with C-ALAL in the case series were alive following treatment. The C-ALAL diagnoses were reported alive (50%) with the remainder designated dead with none reported and unknown (50%). There were no infants with posttreatment status attributed to death in this group. Alive status from C-ALAL accounted for

50.0% of C-ALAL, 1.69% of C-AL, and 0.30% of A-AL. These findings indicated infants diagnosed with C-ALAL in this case series were equally likely to be alive rather than deceased, and those surviving and dying accounted for a mere 0.30% of A-AL.

Approximately three fifths of infants diagnosed with C-OAL in the case series were dead following treatment with the death attributable to this cancer diagnosis. The largest number of C-OAL diagnoses were dead (60.0%) with the remainder alive (20.0%) and unknown classification (20.0%). Death from C-OAL accounted for 60.0% of C-OAL, 5.08% of C-AL, and 0.92% of A-AL. Alive status from C-OAL accounted for 20.0% of C-OAL, 1.69% of C-AL, and 0.30% of A-AL. These findings indicated infants diagnosed with C-OAL in this case series were most likely to be dead rather than alive. Those surviving accounted for a mere 0.30% A-AL, and deaths from C-OAL accounted for 0.92% of A-AL.

Approximately one third of infants diagnosed with I-AML in the case series were dead following treatment with the death attributable to this cancer diagnosis; however, the largest number of I-AML diagnoses were alive (66.4%) with fewer cases dead (31.9%) and unknown (1.77%). Death from I-AML accounted for 31.5% of I-AML, 13.5% of I-AL, and 11.1% of A-AL. Alive status from I-AML accounted for 66.4% of I-AML, 28.2% of I-AL, and 23.1% of A-AL. These findings indicated infants diagnosed with I-AML in this case series were most likely to be alive rather than dead. Those dying accounted for over 11% of A-AL, and those alive accounted for 23.1% of A-AL, meaning approximately 25% of A-AL in the case series survived their diagnoses and were originally diagnosed with I-AML. These findings for I-AML were similar to those in the C-AML group.

Approximately one fourth of infants diagnosed with I-ALL in the case series were dead following treatment with the death attributable to this cancer diagnosis; however, the largest

number of infants with I-ALL diagnoses were alive (68.8%) with fewer cases dead (25.5%) and unknown (5.77%). Death from I-ALL accounted for 25.5% of I-ALL, 13.5% of I-AL, and 25.5% of A-AL. Alive status from I-ALL accounted for 68.8% of I-ALL, 36.4% of I-AL, and 29.9% of A-AL. These findings indicated infants diagnosed with I-ALL in this case series were most likely to be alive rather than dead. Those dying accounted for over 25% of A-AL, and those alive accounted for nearly 30% of A-AL, meaning approximately 30% of A-AL in the case series survived their I-ALL diagnoses and these findings for I-ALL are similar to those in the C-ALL group.

Approximately one half of infants diagnosed with I-ALAL in the case series were dead following treatment with the death attributable to this cancer diagnosis; however, infants with I-ALAL diagnoses were equally reported alive and dead (50.0%), following diagnosis. Death from I-ALAL accounted for 50.0% of I-ALAL, 18.8% of I-AL, and 1.54% of A-AL with identical findings for those who survived (alive). These findings indicated infants diagnosed with I-ALAL in this case series were equally likely to be alive rather than deceased, and those surviving and dying accounted for a mere 1.54% of A-AL. These findings for I-ALAL were similar to those in the C-ALAL group.

Approximately one half of infants diagnosed with I-OAL in the case series were dead following treatment with the death attributable to this cancer diagnosis; however, the I-OAL diagnoses were equally reported alive and dead (50.0%) following diagnosis. Death from I-OAL accounted for 50.0% of I-OAL, 0.75% of I-AL, and 0.62% of A-AL with identical findings for those who survived (alive). These findings indicated infants diagnosed with I-OAL in this case series were equally likely to be alive rather than deceased, and those surviving and dying

accounted for a mere 0.62% of A-AL. The findings for I-OAL were not similar to those in the C-ALAL group as the majority of C-ALAL infants succumbed to the disease following diagnosis.

The cause of death differed significantly between the leukemia lineage age stratified groups, which included congenital and acquired causes of death following treatment for AL. The acute leukemia COD findings in this case series indicated there was limited follow-up information entered into SEER registry for the posttreatment status of infants with AL. In the case series, the binary option of alive or dead was provided, but further classification and/or investigations of the COD was not entered and/or concluded following the death of an infant with AL. Of those COD groups reported, there were 7 diverse types: (a) congenital anomalies, including inherited disorders and/or disorders arising before birth; (b) certain conditions originating in the perinatal period; (c) in situ, benign, or unknown behavior neoplasm; (d) N/A not first tumor; (e) nervous system (brain and other nervous system diseases); (f) infectious and parasitic diseases, including HIV; and (g) pneumonia and influenza.

The majority of C-AL deaths were attributed to congenitally acquired anomalies. The largest number of C-AML diagnoses resulting in death were attributed to congenital anomalies, including inherited disorders and/or disorders arising before birth (3, 8.8% of C-AML), followed by no known status/other (state not available or state DC available but no COD; 2, 5.9% of C-AML), and certain conditions originating in the perinatal period (1, 2.9% of C-AML). C-OAL deaths in the case series were attributed to congenitally acquired anomalies and secondary neoplasms in this case series. The infants with C-ALL diagnoses resulting in death did not provide any further COD information (8, 100.0% of C-ALL). The investigator was not able to evaluate the COD most associated with C-ALL with the findings of the dissertation study. The infants with C-ALAL diagnoses resulting death did not provide any known status/other (state not

available or state DC available, but no COD; 1, 50.0% of C-ALAL) with no posttreatment status for a single infant. The investigator was not able to evaluate the COD most associated with C-ALAL with the findings from the dissertation study. The infants with C-OAL diagnoses resulting in death were attributed to certain conditions originating in the perinatal period (1, 20.0% of C-OAL), in situ, benign, or unknown behavior neoplasm (1, 20.0%), and unknown (1, 20.0% of C-OAL) with one death not attributable to this cancer diagnoses.

The I-AL COD differed significantly across leukemia lineage age stratified groups. The largest number of infants with I-AML diagnoses resulting in death were attributed to no further COD information (32, 88.9% of I-AML). Other CODs included (a) N/A not first tumor (2, 1.8% of I-AML); (b) nervous system (brain and other nervous system diseases; 1, 0.88% of I-AML); and (c) infectious and parasitic diseases, including HIV (1, 0.88% of I-AML). The investigator was not able to evaluate the COD most associated with I-AML diagnosis, given the limited number of diagnoses with the dissertation study findings. There were a diverse number of CODs in the ALL subgroup; however, the largest number of infants with I-ALL diagnoses resulting death were attributed to not reported causes (28, 77.8%). Other I-ALL CODs included (a) N/A not first tumor (2, 0.7% of I-ALL); (b) other cause of death not further categorized (4, 2.8% of I-ALL); (c) infectious and parasitic diseases, including HIV (1, 0.70% of I-ALL); (d) pneumonia and influenza (1, 0.70% of I-ALL); and (e) no known status/other (state not available or state DC available, but no COD; 1, 0.70% of I-ALL). The investigator was not able to evaluate the COD most associated with I-ALL diagnosis with the dissertation study findings, given the limited number of diagnoses. All infants with I-ALAL diagnoses resulting in death were attributed to the provided no further COD information group (5, 100% of I-ALL). The investigator was not able to evaluate the COD most associated with I-ALAL diagnosis with the dissertation study findings,

given the limited number of diagnoses. All infants with I-OAL diagnoses resulting in death were attributed to the provided no further COD information group (1, 50% of I-OAL). The investigator was not able to evaluate the COD most associated with I-ALAL diagnosis with the dissertation findings, given the limited number of diagnoses.

Research Question 3. The characteristics of mortality in AL subgroups differed over time between 2008 to 2014. The majority of deaths after acute leukemia diagnosis were cancer related. There were 109 deaths in the case series, accounting for 33.5% of A-AL with non-cancer related accounting for 21 (19.3% of deaths), and cancer accounting for 80 (73.4% of deaths). The number of infants alive (212) accounted for 65.2% of A-AL, and dead (109) accounted for 33.5% A-AL with no known status/state not available or state DC available, but no COD (4), accounting for 1.2% of A-AL. The range of AL diagnoses across the six-year period from 2008 to 2014 was small and included 42 to 53 diagnoses per year in the case series.

The largest number of AL diagnoses occurred in 2010 (53), which accounted for 16.3% of A-AL, followed by 2014 (48), which accounted for 14.8% of A-AL; 2012 (47), 14.5% of A-AL; 2013 (46), 14.2% of A-AL; 2008 (45), 13.8% of A-AL; 2011 (44), 13.5% of A-AL; and 2009 (42), 12.9% of A-AL. The largest number of diagnoses in 2008 were attributed to alive posttreatment status (29), accounting for 64.4% of 2008 diagnoses with the remaining 16 designated dead (35.5%) attributable to this cancer diagnoses. The largest number of diagnoses in 2009 were attributed to alive posttreatment status (24), accounting for 57.1% of 2009 diagnoses with the remaining 17 designated dead (40.5%). The largest number of diagnoses in 2010 were attributed to alive posttreatment status (29), accounting for 54.7% of 2010 diagnoses with the remaining 23 designated dead (43.4%). The largest number of diagnoses in 2011 were attributed to alive posttreatment status (30), accounting for 68.2% of 2011 diagnoses with the

remaining 14 designated dead (31.8%). The largest number of diagnoses in 2012 were attributed to alive posttreatment status (28), accounting for 59.2% of 2012 diagnoses with the remaining 19 designated dead (40.4%). The largest number of diagnoses in 2013 were attributed to alive posttreatment status (33), accounting for 71.7% of 2013 diagnoses with the remaining 12 designated dead (26.1%). The largest number of diagnoses in 2014 were attributed to alive posttreatment status (39), accounting for 81.3% of 2014 diagnoses with the remaining eight designated dead (16.7%).

The percentage of infants who were designated alive as their posttreatment status from their AL diagnoses fluctuated from 55.8% to 81.3% between 2008 to 2014, including 2008 (29, 64.4%), 2009 (24, 58.5%), 2010 (29, 55.8%), 2011 (30, 68.1%), 2012 (28, 59.6%), 2013 (33, 73.3%), and 2014 (39, 81.3%). The percentage of infants who died from their AL diagnoses fluctuated from 17.0% to 44.2% between 2008 to 2014, including 2008 (16, 35.6%), 2009 (17, 41.4%), 2010 (23, 44.2%), 2011 (14, 31.8%), 2012 (19, 40.4%), 2013 (12, 26.7%), and 2014 (8, 16.7%).

In 2008, there were 45 infants diagnosed (13.8% of AL), and 35.6% with death outcome, which accounted for 14.7% of all A-AL deaths in the case series ($N = 109$). In 2009, there were 42 infants diagnosed (12.9% of AL), and 41.4% with death outcome, which accounted for 15.6% of all deaths in the case series. In 2010, there were 53 infants diagnosed (16.3% of AL), and 44.2% with death outcome, which accounted for 21.1% of all deaths in the case series. In 2011, there were 44 infants diagnosed (13.5% of AL), and 31.8% with death outcome, which accounted for 12.8% of all deaths in the case series. In 2012, there were 47 infants diagnosed (14.5% of AL), and 40.4% with death outcome, which accounted for 17.4% of all deaths in the case series. In 2013, there were 46 infants diagnosed (14.2% of AL), and 26.7% with death

outcome, which accounted for 11.0% of all deaths in the case series. In 2014, there were 48 infants diagnosed (14.8% of AL) with the lowest percentage of deaths in a diagnosis year (8,16.7%), which accounted for 7.34% of all deaths in the case series.

Research Question 3.1. The number of diagnoses in age stratified congenital and infant AL subgroups differed little over time between 2008 to 2014. Over the six-year period, the diagnosis ranged from 42 to 53 cases during 2008 to 2014. The largest number of diagnoses (53) occurred in 2010 and the fewest (42) in 2009. The characteristics of posttreatment status, including alive, dead, or unknown, in age stratified congenital and infant AL subgroups differed over time between 2008 to 2014.

The evaluation of the association between year of diagnosis and the type of AL using the chi-square test ($\alpha = 0.05$), $X^2 = 33.51$, $p = .822$ indicated there was no statistically significant relationship between year of diagnosis in the case series and AL lineage. Infants were equally likely to be diagnosed from 2008 to 2014 in all AL groups: C-AML, C-ALL, C-ALAL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, or I-OAL.

These findings indicated the range of AL posttreatment status across the six-year period from 2008 to 2014 fluctuated from the alive (54.7%-81.3%) and dead (16.7%-43.3%). In 2014, the last year of the cases series, the least number of children died from AL with an increase over the six-year period, and the number of deaths began to fall from the peak deaths (40.5%-43.4%) down to a mere 16.7%; further studies would be necessary to confirm the findings as there was a continued reduction in deaths over time. More children survived than died from AL with an increase over time as reported in this case series. It was assumed advancement in detection methodologies over time would result in a reduced number of deaths from AL. The increased ability to detect and treat the disease should reduce the number of deaths from the disease. These

findings indicated that the majority of infants diagnosed with AL in the case series were alive at most recent update the SEER registry data (April 16, 2018) prior to access of case series record data for this dissertation study.

In 2008, reports included C-AML, C-ALL, C-OAL, and I-AML; there were no reports of C-ALAL, I-ALAL, or I-OAL. Of the 45 infants diagnosed in 2008, the majority were alive following treatment (29, 64.4%) with fewer cases deceased (16, 35.6%). However, in 2008, infants with diagnoses of C-AML or C-ALL were most likely to die following treatment than survive. Comparatively, infants with diagnoses of I-AML and I-ALL had much better outcome data with alive after treatment 3.25 and 2.85 times more likely than death in I-AML in I-ALL, respectively. These findings indicated more children overall were alive than dead following treatment in 2008. The majority of infants with C-AML diagnoses in 2008 were dead (3) rather than alive (1) following treatment. The majority of infants with C-ALL diagnoses in 2008 were dead (3) rather than alive (1) following treatment. The majority of infants with I-AML diagnoses in 2008 were alive (13) rather than dead (4) following treatment. The majority of infants with I-ALL diagnoses in 2008 were alive (20) rather than dead (7) following treatment. A single infant with C-OAL diagnosis was reported posttreatment status in 2008 as alive following treatment. There was limited information regarding the diagnoses of infants with C-OAL with a single case resulting in survival; C-ALAL, I-ALAL, and I-OAL were not reported, and this finding made interpretation of outcomes for these subgroups limited in this diagnostic year within the case series.

In 2009, reports included C-AML, C-ALL, C-ALAL, I-ALL, I-ALAL, and I-AML; there were no reports of C-OAL or I-OAL. Of the 42 infants diagnosed in 2009, the majority were alive following treatment (24, 58.5%) as compared with those deceased (17, 41.4%). However,

in 2009, diagnoses of infants with C-ALL were most likely to die following treatment than survive. In children with a diagnosis of C-AML and I-AML, an outcome of alive following treatment was only slightly more likely than death. Comparatively, infants with I-ALL diagnoses had much better outcome data with alive after treatment 1.6 times more likely than death. These findings indicated that overall, more children were alive following treatment in 2009. The majority of infants with C-AML diagnoses in 2009 were alive (3) rather than dead (2) following treatment. The majority of infants with C-ALL diagnoses in 2008 were dead (2) rather than alive (1) following treatment. A single infant with C-ALAL diagnoses indicted a posttreatment status in 2009 as state DC not available or state DC available but no COD following treatment. The majority of infants with I-AML diagnoses in 2009 were alive (7) rather than dead (6) following treatment. The majority of infants with I-ALL diagnoses in 2009 were alive (11) rather than dead (7) following treatment. Two cases of infants with I-ALAL diagnoses in 2009 were alive following treatment; there were no deaths in infants with I-ALAL reported in 2009. There was limited information regarding the diagnoses of infants with C-ALAL and I-ALAL with a single case resulting in death and two cases alive, respectively; C-OAL and I-OAL were not reported, which made interpretation of outcomes for these subgroups limited in this diagnostic year within the case series.

In 2010, reports included C-AML, C-ALL, C-OAL, I-AML, I-ALL, and I-ALAL; there were no reports of C-ALAL or I-OAL. These findings indicated that overall, more children were alive following treatment with fewer children who succumbed to disease. Of the 53 diagnoses in 2010, the majority were alive following treatment (29, 55.8%) with fewer cases deceased (23, 44.2%). In 2010, diagnoses of infants with C-AML were most likely to survive following treatment than die as all cases were reported with this outcome. In children with a diagnosis of I-

AML, an outcome of alive following treatment was only slightly more likely than death with a 1.1 times more likely outcome. All cases of infants with C-AML diagnoses in 2010 were alive (4) following treatment. All cases of infants with C-ALL diagnoses in 2010 were dead (1) following treatment. The single case of an infant with C-OAL diagnosis in 2010 was dead following treatment. The majority of infants with I-AML diagnoses in 2010 were alive (14) rather than dead (12) following treatment. The majority of infants with I-ALL diagnoses in 2010 were alive (19) rather than dead (10) with a single case that was reported posttreatment status in 2010 as state DC not available or state DC available but no COD following treatment. The single case of an infant with I-ALAL diagnosis in 2010 was dead following treatment. There was limited information regarding the diagnoses of infants with C-ALL and C-OAL with a single case resulting in death in each group, respectively; infants with C-ALAL or I-OAL were not reported, which made interpretation of outcomes for these groups limited in this diagnostic year within the case series. Comparatively, diagnoses of infants with I-ALL had much better outcome data with alive after treatment 1.9 times more likely than death.

In 2011, reports included C-AML, C-ALL, I-AML, I-ALL, I-ALAL, and I-OAL; there were no reports of C-ALAL or C-OAL. These findings indicated that overall, more children were alive, approximately two times more, following treatment with fewer cases of children who succumbed to disease in 2011. In children with a diagnosis of C-AML, C-ALL, or I-ALAL, an outcome of alive following treatment was only slightly more likely than death. Comparatively, diagnoses of infants with I-AML and I-ALL had much better outcome data with alive after treatment (4) and 2.28 times more likely than death in infants with I-AML and I-ALL, respectively. Of the 44 infants diagnosed in 2011, the majority were alive following treatment (30, 68.1%) with the remainder deceased (14, 31.8%). The majority of infants with C-AML

diagnoses in 2011 were alive (3) rather than dead (2) following treatment. The majority of infants with C-ALL diagnoses in 2011 were alive (2) rather than dead (1) following treatment. The majority of infants with I-AML diagnoses in 2011 were alive (8) rather than dead (2) following treatment. The majority of infants with I-ALL diagnoses in 2011 were alive (16) rather than dead (7) following treatment. The majority of infants with I-ALAL diagnoses in 2011 were alive (2) rather than dead (1) following treatment. The single case of an infant with I-OAL diagnosis in 2011 was dead following treatment. There was limited information regarding the diagnoses of I-OAL with a single case resulting in death; C-OAL and C-OAL were not reported, which made interpretation of outcomes for these subgroups limited in this diagnostic year within the case series.

In 2012, reports included C-AML, C-ALL, C-OAL, I-AML, I-ALL, and I-ALAL; there were no reports of C-ALAL or I-OAL. Of the 47 infants diagnosed in 2012, the majority were alive following treatment (28, 59.6%) with the remainder deceased (19, 40.4%). These findings indicated that overall, more children were alive following treatment in 2012. In children with a diagnosis of C-AML, an outcome of alive following treatment was only slightly more likely than death. Infants with C-ALL diagnoses were three times more likely to be alive with fewer cases dead following treatment. Comparatively, diagnoses of infants with I-AML and I-ALL had much better outcome data with alive after treatment four and 2.67 times more likely than death in infants with I-AML and I-ALL, respectively. The majority of infants with C-AML diagnoses in 2012 were alive (3) rather than dead (2) following treatment. The majority of infants with C-ALL diagnoses in 2012 were alive (3) rather than dead (1) following treatment. The majority of infants with I-AML diagnoses in 2011 were alive (8) rather than dead (2) following treatment. The majority of infants with I-ALL diagnoses in 2012 were alive (16) rather than dead (6)

following treatment. The single case of an infant with I-ALAL diagnosis in 2012 was dead following treatment. The single case of an infant with I-OAL diagnosis in 2011 was dead following treatment. The single case of an infant with C-OAL diagnosis in 2012 was dead following treatment. The majority of infants with I-AML diagnoses in 2012 were dead (8) rather than alive (6) following treatment. The majority of infants with I-ALL diagnoses in 2012 were alive (16) rather than dead (6) following treatment. The majority of infants with I-ALAL diagnoses in 2012 were alive (2) rather than dead (1) following treatment with a single case posttreatment status in 2010 that was reported as state DC not available or state DC available but no COD following treatment. There was limited information regarding the diagnoses of C-OAL I-ALAL with a single case resulting in death in each group, respectively; C-ALAL and I-OAL were not reported, which made interpretation of outcomes for these subgroups limited in this diagnostic year within the case series.

In 2013, reports included C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL. Of the 46 infants diagnosed in 2013, the majority were alive following treatment (33, 73.3%) with fewer cases deceased (12, 26.7%). These findings indicated that overall, more children were alive, approximately 2.75 times more, following treatment with fewer cases of children who succumbed to disease in 2013. In children with a diagnosis of C-ALL and I-ALAL, an outcome of alive following treatment was only slightly more likely than death. All infants with I-OAL diagnoses were alive unlike infants with C-OAL diagnoses, which resulted in death for all. Comparatively, diagnoses of infants with C-AML, I-AML, and I-ALL had much better outcome data with alive after treatment five, 4.5, and 5.3 times more likely than death, respectively. The majority of infants with C-AML diagnoses in 2013 were alive (5) rather than dead (1) following treatment. The infants with C-ALL diagnoses in 2013 were equally

designated alive (2) and dead (1) following treatment. The single infant with C-ALAL diagnosis in 2013 was dead following treatment, and the other reported no posttreatment status. All cases of infants with C-OAL diagnoses in 2013 were dead (2) following treatment. The majority of infants with I-AML diagnoses in 2013 were alive (9) rather than dead (2) following treatment. The majority of infants with I-ALL diagnoses in 2013 were alive (16) rather than dead (3) following treatment. The majority of infants with I-ALAL diagnoses in 2011 were alive (2) rather than dead (1) with a single case posttreatment status in 2010 that was reported as state DC not available or state DC available but no COD following treatment. The single case of an infant with I-OAL diagnosis in 2011 was alive following treatment. There was limited information regarding the diagnoses of infants with C-ALAL and I-ALAL with a single case resulting in death in each group, respectively; C-ALAL and I-OAL were not reported, which made interpretation of outcomes for these subgroups limited in this diagnostic year within the case series.

In 2014, reports included C-AML, C-ALL, I-AML, I-ALL, and I-ALAL; there were no diagnosis of infants with C-ALAL, C-OAL or I-OAL. Of the 48 infants diagnosed in 2008, the majority were alive following treatment (39, 81.3%) with fewer deceased (16, 35.6%). These findings indicated that overall, more children were alive rather than dead, approximately three times more, following treatment in 2014. In children with a diagnosis of C-ALL and I-ALAL, an outcome of alive following treatment was only slightly more likely than death. All infants with C-AML and C-ALL diagnoses were alive following diagnosis, making this outcome the most likely for children with these AL lineage age groups. Comparatively, diagnoses of infants with I-AML and I-ALL had much better outcome data with alive after treatment 5.6, and three times more likely than death, respectively. All cases of infants with C-AML diagnoses in 2014 were

alive (3) following treatment. All cases of infants with C-ALL diagnoses in 2014 were alive (3) following treatment. The majority of infants with I-AML diagnoses in 2014 were alive (17) rather than dead (3) following treatment. The majority of infants with I-ALL diagnoses in 2014 were alive (15) rather than dead (5) following treatment. The single case of an infant with I-ALAL diagnosis in 2011 was alive following treatment. There was limited information regarding the diagnoses of infants with I-ALAL with a single case that was reported with a survival outcome; C-ALAL, C-OAL, and I-OAL were not reported, making interpretation of outcomes for these subgroups limited in this diagnostic year within the case series.

Research Question 3.2. There was little difference in treatment administered to congenital and infant AL; however, differences emerged following lineage stratification of the case series over the six-year period. Approximately 90% of cases were administered chemotherapy. Radiation was administered in under 4% of patients with a small fraction (0.6%) without the report of the radiation method administered if designated, and over 95% of patients were not administered beam radiation. The evaluation of the association between treatment administered and the type of AL using the chi-square test ($\alpha = 0.05$), $X^2 = 37.45$, $p < .05$ indicated there was a statistically significant relationship between treatment administered and AL lineage. The hypothesis of the test that treatment type administered would be significantly related to leukemia lineage group diagnosed, and the null was rejected in favor of the alternative. Infants were most likely to be treated with chemotherapy following diagnosis in all AL groups: C-AML, C-ALL, C-ALAL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, or I-OAL. There was treatment preference (chemotherapy vs. beam radiation) for AL in the case series. These findings have confirmed alignment of treatment protocols for infants diagnosed with AL with international treatment protocols for this population; treatments were administered aligned to these algorithms,

and there was unlikely to be changes that would affect overall outcomes for infants in this case series (Pieters et al., 2007). These findings were consistent with international treatment protocols for infants younger than 1 year of age. Chemotherapy regimens are generally administered with irradiation administration, generally reserved only for the highest risk patients, given concern over late neuropsychological toxicity resulting from administration (Pieters et al., 2007).

These findings indicated the majority of C-AML and nearly all cases of C-ALL were treated with chemotherapy regimens. Comparatively, cases of C-ALAL were treated with chemotherapy regimens, but patients may have elected not to administer treatment, and cases of C-OAL were more likely to be treated with chemotherapy regimens than no treatment. Nearly all cases of I-AML, I-ALL, and I-ALAL were treated with chemotherapy regimens. Cases of I-OAL were treated with chemotherapy regimens, but patients may have elected not to administer treatment.

The largest number of infants with C-AML diagnoses were administered chemotherapy (22, 64.7%) with fewer cases not administered (12, 35.2%). There were no infants administered beam radiation, and all infants were assigned to the subgroup no radiation and/or cancer-directed surgery administered. The largest number of infants with C-ALL diagnoses were administered chemotherapy (17, 94.4%) with fewer cases not administered (1, 0.56%). There were no C-AL infants administered beam radiation, and all infants were assigned to the subgroup no radiation and/or cancer-directed surgery administered. Diagnoses of infants with C-ALAL were equally likely to be administered chemotherapy (1, 50.0%) and not administered (1, 0.50%). Both infants were designated no/unknown administered beam radiation but were assigned to the subgroup no radiation and/or cancer-directed surgery administered, and it was presumed they were not administered radiation. The largest number of infants with C-OAL diagnoses were administered

chemotherapy (3, 60.0%) with fewer cases not administered (2, 40.0%). There were no infants administered beam radiation, and all infants were assigned to the subgroup no radiation and/or cancer-directed surgery administered.

The largest number of infants with I-AML diagnoses were administered chemotherapy (104, 92.0%) with fewer cases not administered (12, 10.6%). Under 4% of infants (4, 3.54%) were administered beam radiation, and all infants were assigned to the subgroup no radiation and/or cancer-directed surgery administered, and it was presumed they were not administered radiation. The largest number of infants with I-ALL diagnoses were administered chemotherapy (133, 94.3%) with fewer cases not administered (8, 5.7%). Under 4% of infants (4, 3.54%) administered beam radiation, and all infants were assigned to the subgroup no radiation and/or cancer-directed surgery administered, and it was presumed they were not administered radiation. The largest number of infants with I-ALAL diagnoses were administered chemotherapy (9, 90.0%) with fewer cases not administered (1, 10%). There were 30% of infants (3, 30%) administered beam radiation, and all infants were assigned to the subgroup no radiation and/or cancer-directed surgery administered, and it was presumed they were not administered radiation. Diagnoses of infants with I-OAL were equally likely to be administered chemotherapy (1, 50.0%) and not administered (1, 0.50%). One infant was designated no/unknown and administered beam radiation, but both infants were assigned to the subgroup no radiation and/or cancer-directed surgery administered, and it was presumed they were not administered radiation.

Research Question 4 and 5. The generation of new pathology subgroups of congenital and infant lineage stratified leukemia resulting from this dissertation study can generate new laboratory testing algorithms that appropriately utilize laboratory tests that provide non-specific and specific results to aid in diagnosis and management if infants with acute leukemia. The 2017

CAP and ASH "Initial Diagnostic Workup of Acute Leukemia" present an excellent reference for the appropriate steps to be taken through cooperation between the clinicians, pathologists, and laboratory medicine professionals to ensure an accurate diagnosis of patients (Arber et al., 2017). Although not inclusive of all appropriate testing, the CAP/ASH workup dictates the primary steps to providing an accurate diagnosis include the comprehensive sharing and reporting of data, including (a) age; (b) sex; (c) ethnicity; (d) history of any hematological disorder or known predisposing conditions or syndromes; (e) prior malignancy; (f) exposure to cytotoxic therapy, immunotherapy, radiotherapy, or other possibly toxic substances; (g) any history of possibly confounding factors (e.g. growth factor therapy, or other medication that mimic the features of acute leukemia); (h) family history of any hematologic disorder or other malignancies; (i) relevant physical examination, imaging, or other tissue findings; and (j) all other clinical findings with diagnostic of prognostic importance (Arber et al., 2017). The sharing of the relevant clinical data that are readily accessible to pathologists and laboratory medicine professionals is critical to selecting the appropriate tests, allowing for timely reporting and interpretation of the results back to the referring clinician (Arber et al., 2017). All suspected or confirmed leukemia should be evaluated using the following laboratory techniques per the ASH/CAP guideline: (a) complete blood counts; (b) morphological evaluation; (c) conventional cytogenetic analysis; (d) molecular, genetic, and/or fluorescent in situ hybridization testing; (e) flow cytometric immunophenotyping; and (f) histochemistry (Arber et al., 2017). Using these techniques, a diagnosis of acute leukemia should be confirmed or ruled out prior to initiating further studies (Arber et al., 2017). Guidance for subsequent genetic testing in the AML, ALL, and ALAL is stratified by the age of the population under evaluation (adults and pediatric groups); however, this guidance fails to differentiate testing differences for pediatric versus

infant populations; there was no mention of OAL that failed to be defined by laboratory medicine and pathology testing strategies in ASH or American Society of Clinical Medical Genetics and Genomics Clinical Genetics Laboratories guidance (ACMG, 2018; Arber et al., 2017). Given the findings of this dissertation study, there should be further evaluation of OAL given this lack of data to assist in testing in the less than 12 month AL infant population and the need to further stratify this group into one of the other subtypes with yet to be identified characteristics.

The current ASH and ACMG B-ALL pediatric testing indicates testing should be performed for: (a) t(12;21)(p13.2;q22.1); *ETV6-RUNX1*; (b) t(9;22)(q34.1;q11.2); *BCR-ABL1;* (c) KMT2A(MLL) rearrangement; (d) iAMP21 (inter-chromosomal amplification of chromosome 21); and (e) trisomy 4 and 10 with the optional request of molecular genetic mutational analysis. This guidance is for all pediatric patients with most laboratories implementing standard operating procedures (SOPs) to ensure these tests are tailored to the age groups under evaluation (ACMG, 2018; Arber et al., 2017). These SOPs should take the findings of this dissertation study and other studies into consideration to ensure tests are appropriately evaluated for use in this population and are inclusive of the following changes suggested discussed herein.

However, the findings of this dissertation study of infants less than 12 months of age indicated there were no designations of "B-lymphoblastic and leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1*" or "B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*." This investigator confirmed previous data that suggest "B-lymphoblastic and leukemia/lymphoma with (9;22)(q34.1;q11.2); *BCR-ABL1*" accounted for approximately 25% of adult ALL, but is very rare in of childhood cases (2%-4%) with limited

information and reports in the infant group of "B-lymphoblastic and leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*," which is known to account for 25% of childhood leukemia, but is not observed in infants (Swerdlow et al., 2017). The testing for iAMP21 (inter-chromosomal amplification of chromosome 21), although not detected in this dissertation study nor is a WHO 2017 defined subgroup of acute leukemia, can have diagnostic and prognostic impact; yet, given the lack of finding in this dissertation study and previous reports of the median age of this abnormality in pediatric leukemia of 9 years and not infant leukemia, it is not suggested as a tool to aid in the diagnosis of the less than 12 month population (Harrison, 2015). However, it is important to note this abnormality would likely be detected given abnormalities of chromosome 21 can often be detected using t(v;21) probe testing. The testing for trisomy 4 and 10 accounted for a single diagnosis in this case series, and this investigator confirmed that this subtype is a subtype of ALL not generally observed in the less than 12 month infant population; however, as it is associated with a hyperdiploid karyotype and favorable prognosis, testing may still be performed in the absence of other molecular markers to provide diagnostic or prognostic information (Swerdlow et al., 2017). Testing for "t(1;19)(q23;p13.3); *TCF3-PBX1*" is not indicated specifically in the ASH or ACMG guidelines and is a WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2017 subtype, known to be more frequent in children, but accounted for a single diagnosis in this dissertation study and should be included in the standard workup. The "B-lymphoblastic and leukemia/lymphoma, *BCR-ABL1-like*," a WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2017 defined subgroup, was not observed in this case series given it cannot be coded for but is a very new category and may have a higher incidence than reported, given newly recommended testing for "B-lymphoblastic and leukemia/lymphoma, *BCR-ABL1-like*," which includes FISH testing of a

variety of abnormalities that may not be currently detected in routine work of infants less than 12 months of age: (a) *CRLF2* rearrangement, (b) *PDGFRB* (5q33) rearrangement, (c) *CDKN2A/B* (9p21.3) deletion, and (d) *PAX5* (9p13.2) deletion. These findings indicated *BCR-ABL1-like* testing should be introduced into the workup of infant acute leukemia. The third test would suggest to the clinician KMT2A (MLL) rearrangement should and is often the first test performed in infants less than 12 months of age by the clinical genetics laboratory. This investigator confirmed this strategy in testing as the B-lymphoblastic and leukemia/lymphoma with recurrent genetic abnormalities group of ALL was dominated by "B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A rearranged*" subtype diagnoses in this case series. These testing strategies and the findings of this dissertation study were confirmed in previous reports that *KMT2A* translocations have a high incidence, although not 90% as reported previously in infants less than 12 months of age with over 120 different translocation partners identified to date. Given the cryptic nature of these *KMT2A* abnormalities, they should be evaluated using FISH at diagnosis, and this finding was consistent with ACMG guidance that does not allow cytogenetic karyotyping for new AL specimens to be the only assay used in the workup. Together these findings indicated testing for "t(12;21)(p13.2;q22.1); *ETV6-RUNX1,*" "t(9;22)(q34.1;q11.2); *BCR-ABL1,*" iAMP21,and trisomy of chromosomes 4 and 10 may not be appropriate to select as primary testing in the infant less than 12 months age group, rather *KMT2A* translocations should be tested in all infants with ALL less than 12 months of age first before proceeding to other testing strategies. This strategy is current standard practice in many but not all clinical laboratories.

Sadly, the largest group of infants were placed into the "B-lymphoblastic and leukemia/lymphoma, NOS," accounting for nearly 80% of diagnoses as this is a group currently

defined by a lack of currently known genetic markers to differentiate the ALL into specific group. Initial studies may include additional FISH to detect the rarer groups "t(1;19)(q23;p13.3); *TCF3-PBX1*", but it is clear more studies are needed for yet to be identified genetic markers to guide laboratory medicine- and pathology-based diagnoses for this group of ALL.

In the current ASH and ACMG T-ALL testing strategies there was no stratification of adult versus pediatric populations nor differentiation for infant testing strategies; however, the findings of this dissertation study indicated T-lymphoblastic leukemia/lymphoma accounted for approximately 3.69% of the cases series and was consistent with previous reports that it is more common in adolescents than in younger children. This subgroup is not currently stratified by this dissertation study with useful genetic findings; however, ACMG guidelines suggested all T-ALL be tested for "t(9;22)(q34.1;q11.2); *BCR-ABL1*" and KMT2A (MLL) rearrangement. Given the rare finding of infant T-ALL, testing of these two markers will continue while more studies are conducted to identify markers to guide laboratory medicine- and pathology-based diagnoses of this subgroup.

In the current ASH guidance, the ALAL subtype mixed phenotype acute leukemia testing does not differentiate between adults and pediatric patients; however, it indicates testing should be performed for t(9;22)(q34.1;q11.2); *BCR-ABL1* 2) KMT2A (MLL) rearrangement. The ACMG guidance does not differentiate ALAL from other subgroups of AL for testing strategies (ACMG, 2018; Arber et al., 2017). However, in this dissertation study of infants less than 12 months of age, there were no designations of mixed phenotype acute leukemia with "t(9;22)(q34.1;11.2); *BCR-ABL1*." Comparatively, mixed phenotype acute leukemia with "t(v;11q23.3); *KMT2A* rearranged," accounted for one fourth of ALAL diagnoses, which suggested this should be tested for in the less than 12 months of age population. Sadly, the

largest group of infants were placed into the mixed phenotype acute leukemia with B/myeloid, NOS; acute undifferentiated leukemia; and mixed phenotype acute leukemia with T/myeloid, NOS subgroups, accounting for 75% of diagnoses. As this subgroup is one currently defined by a lack of current genetic markers to differentiate ALAL into specific subtypes, testing should continue with the rarely recognized genetic markers, but it is clear more studies are needed for yet to be identified markers to guide laboratory medicine and pathology based diagnoses.

The current ASH and ACMG AML testing guidelines first separate APML or APL (*PML-RARA*) from other AML for rapid testing of this subtype due to the risk of disseminated intravascular coagulation and rapid death for these patients (ACMG, 2018; Arber et al., 2017). In this dissertation study, the APL with *PML-RARA* subgroup accounted for a mere 0.62% of the cases series, a single case in the C-AML, and I-AML groups, respectively. This finding was consistent with previous reports of *PML-RARA* translocations in acute leukemia with the highest incidence in younger adults but should remain a part of testing algorithms given the nature of presentation and the prognostic impact to infants with this leukemia subtype (Chen et al., 2012).

The ASH and ACMG AML testing subsequently recommends subdivision of AML into two groups: core binding factor (CBF) AML, including "t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*" and "AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*" and AML other than CBF, APML (APL), or AML with myelodysplasia-related cytogenetic abnormalities (ACMG, 2018; Arber et al., 2017). However, in the findings of this dissertation, in the study of infants less than 12 months of age, there were no designations of "t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*." This investigator confirmed previous data, suggesting "t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*" accounts for a mere approximately 1% to 5% of all acute leukemia primarily in younger adult patients and not children (Swerdlow et al., 2017). "AML with inv(16)(p13.1q22) or

t(16;16)(p13.1;q22); *CBFB-MYH11*" accounted for a single diagnosis in this case series, and the findings of this dissertation study were consistent with previous reports of *CBFB-MYH11* translocations found mainly in adults with rare cases documented in infants (Poddighe et al., 2018). As CBF AML often have suggestive morphology to guide the selection of the appropriate genetic testing, testing strategies in the infant population should be guided through combination of this information in the clinic.

The second group, AML other than CBF, APL, or AML with myelodysplasia-related cytogenetic abnormalities, would be the appropriate group testing strategy for the majority of diagnoses; however, given the vast nature of cytogenetic and molecular genetic changes, there were no suggested testing strategies in the ASH guide. The ACMG guidelines did not differentiate pediatric from adult populations; however, ACMG indicated testing should include *KMT2A* (MLL) rearrangement on all diagnostic AML specimens, given the cryptic nature of these abnormalities. The testing of *KMT2A* (MLL) rearrangement should and is often the first test performed in infants less than 12 months of age. This investigator confirmed this strategy in testing as the AML with recurrent genetic abnormalities group of AML was dominated by "AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL) *variant KMT2A translocations in acute leukemia*" subtype diagnoses. These testing strategies and the findings of this dissertation study that AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL) *variant KMT2A translocations in acute leukemia"* accounted for 7% to 8% of C-AML and I-AML, suggesting this strategy should be tested for in the less than 12 month of age AML population. This investigator confirmed previous reports that *KMT2A* translocations have a high incidence (90%) in infants with a slightly lower incidence in the less than 12 months of age groups. There are over 120 different known translocation partners identified to date and given the cryptic nature of these

abnormalities, they should be evaluated using FISH at diagnosis. The "AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*" subtype, although not suggested in ACMG guidelines, accounted for a single diagnosis in this population and should be tested for in infants without an informative karyotypes using FISH testing.

Sadly, the largest groups of infants were placed into AML not otherwise specified (NOS) subgroup, accounting for 40% of diagnoses. This group is currently defined by a lack of current markers to differentiate the AML into specific subtypes, and testing should continue with the rarely recognized genetic markers, but it is clear more studies are needed for yet to be identified markers to guide laboratory medicine- and pathology-based diagnoses.

The ACMG guidelines rely heavily on conventional karyotyping and reflex to applicable FISH probes to detect other WHO defined cytogenetics subtypes (ACMG, 2018). The findings of this dissertation indicated these groups in the less than 12 months of age infant population are "AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*" and "AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL) *variant KMT2A translocations*." However, acute monoblastic and monocytic leukemia accounted for less than 10% of AL. Acute myelomonocytic leukemia accounted for under 5% of I-AML. Acute megakaryoblastic leukemia subtype, although not defined by a single cytogenetic abnormality, does have known recurrent abnormalities that can assist in further stratification of patients in the diagnostic workup and may be included in future subgroups of infant acute leukemia. In the event chromosome analysis is unsuccessful, FISH probes (if available) may be selected for infants with AML. These findings indicated testing for "t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*," "AML with t(6;9)(p23;q34.1); *DEK-NUP214*," "AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*," and AML with *BCR-ABL1* may not be appropriate to select as primary testing in the infant less than

12 month of age group. AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*(MLL) *variant KMT2A translocations,*" *PML-RARA*, "inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*," and karyotyping are used to detect other cytogenetic defined subgroups and should be tested for in all infants with AML less than 12 months of age. Laboratories should take the findings of this dissertation study and other studies into account to ensure tests are appropriate to evaluate recurrent cytogenetic subtypes of AML and previously undefined groups to aid in the appropriate diagnosis of infants with AML.

Literature Review

An age-based stratification of ALL and AML in the infant, pediatric, and adult populations has been reported throughout the medical literature. ALL is considered a disease of the young, whereas AML patients are generally significantly older adults. However, in infants less than 12 months of age at diagnosis, this age-based stratification changes across birth to 12 months with more AML cases reported in congenital (birth to < 2 months), fewer reported in ALL, and more ALL cases reported in the infant (≥ 2 months to < 12 months) compared with fewer in AML with AML the majority of diagnoses in the entire group. This investigator confirmed the findings of previous studies that suggested ALL dominates diagnoses in older infants with fewer cases of AML; however, in the congenital leukemia population, AML dominates ALL in diagnoses (Aier et al., 2002; Bajwa et al., 2004; Brown, 2009; Campos et al., 2011; Özdemir, 2002; Raj et al., 2014; Shah et al., 2003; Sung et al., 2010; Wiemels, 2012).

This investigator confirmed the findings of previous studies by Bresters et al. (2002) and Issacs (2003), which indicated AML dominated the C-AL diagnoses rather than ALL. Specifically, this investigator found C-AML at a near double percentage to C-ALL, (57.6% of C-AL vs. 30.5%, respectively) just as Bresters et al. (2002) and Issacs (2003) reported in their reviews of 117 and

145 patient records, respectively, with 56% to 64% of C-AL attributed to C-AML versus 21% to 38% C-ALL. In comparison, Cao et al. (2015) included a 10-year review of Mayo Clinic Cytogenetics Database acute leukemia diagnoses in infants less than 12 months, limited to 85 cases, and concluded C-AL is rare in comparison to I-AL, but in this cohort, C-AML and C-ALL occurred in a mere six cases each. This dissertation study is a larger case series and is more recent than the studies by Bresters et al. (2002) and Issacs (2003), and it is in keeping with these findings, but is in conflict with the Cao et al. (2015) study. This conflict with the Cao et al. (2015) study is acceptable and not unexpected as their study may have been limited due to a small number of cases that had been referred to a large reference laboratory center, which may have generated bias in the cases reported, whereas this dissertation study included cases reported across the country. The findings in this dissertation study of a higher frequency of AML in the C-AL population was consistent with the earliest reports of infant and congenital leukemia in the medical literature (Bernhard et al., 1951; Bresters et al., 2002; Heerema et al., 1999; Isaacs, 2003; O'Connor et al., 1954; Pui, 2012; Resnik et al., 2009; Resnik & Brod, 1993; Wolk et al., 1974). Although previous studies were used to evaluate AML, ALL, and ALAL, they did not stratify the population by age. The findings of this dissertation study indicated AML, ALL, and ALAL were more common in I-AL, whereas OAL or undefined leukemia was most common in C-AL, a finding not documented in previous studies.

Bresters et al. (2002) indicated there was no statistically significant difference between the sexes reported for diagnoses of acute leukemia, but in early literature, more boys were likely to be diagnosed than girls. This investigator confirmed the finding of Bresters et al. (2002) and concluded there was no statistically significant relationship between sex of record and leukemia lineage age group, meaning C-AML, C-ALL, C-ALAL, C-OAL, I-AML, I-ALL, I-ALAL, and I-OAL were

equally likely to be diagnosed in females and males. These previous studies, unlike this dissertation study and the studies of Bresters et al. (2002), failed to stratify acute leukemia by age less than 12 months, which may have contributed to the higher incidence of males versus females for ALL and AML in the larger age range infant population (Bresters et al., 2002; Isaacs, 2003; Redaelli et al., 2005).

Implications

Implications for Practice

The standard workup for infants with a query leukemia is currently very close to that of presentation evaluation of acute leukemia in older children; however, as this investigator and others suggested, infant leukemia is a unique entity. This differentiation of the disease in younger children is a must in clinical diagnostic pathology to provide the best care for children at initial diagnosis and follow-up. Recognizing the candidate WHO defined subtypes of leukemia, including any and all of the genetic findings, is critical to ensure that patients are placed into the correct diagnostic and prognostic groups. These groups are used to risk stratify, determine the aggressiveness of treatment plans, and/or to choose not to administer care. Diagnosis must be accurate as the consequences of issuing an inaccurate report can be fatal.

Given the rarity of infant leukemia, not all clinicians or laboratory medicine and pathology professionals will encounter an infant leukemia during routine work, but guidance must exist to ensure these patients receive the best care possible. The hematological profile of infants during the first months of life is difficult as many blood parameters change dramatically from birth to 1 month of age. There are unique complications in the evaluation of preterm infants, and the overlapping presentation of AL with numerous constitutional (inherited) disorders of hematopoietic cell production and survival hinder the ability to make a timely and

accurate diagnosis. Robust standards of practice in neonatal hematology oncology must address how best to detect these emergent cases, which will include a revision to current genetic testing strategies to a strategy based algorithm of karyotyping with sequential and rapid FISH testing based on WHO defined subgroups specific to the AL lineage most likely only.

The standards of care are constantly changing, and the majority of infant leukemia remain unstratified. Further research on the genetic abnormalities in infant populations must be quickly addressed in the clinical laboratory once discovered to have diagnostic and prognostic utility.

Implications for Further Research

Further investigations are needed for the classification of infant leukemia in order to drive the identification of new treatment protocols for infants because there are increases in the overall survival rates for pediatric cancers, nearly 20% of pediatric cancer patients cannot be treated effectively with current treatments and eventually die from disease (NCI, 2018). Infant acute leukemia remains one of the deadliest forms of pediatric cancer, and as confirmed by this investigator, a significant portion (~34% of infants) eventually succumb to their disease (NCI, 2018). However, those who do survive must live with severe short-term and long-term effects of the therapies that includes the risk for secondary cancers, developmental delay, infertility, and even physical and emotional health issues (NCI, 2018). Additional research into these rare leukemia have promise to uncover additional MPE characteristics that are involved in the initiation of uncontrolled cell growth that subsequently lead to malignant transformation and reaching these targets with new therapies may change the landscape of infant leukemia diagnoses and outcomes.

Limitations and Delimitations

Limitations

Data collected by the NCI SEER database represented approximately 28% of the U.S. population, and the utilization of only the SEER 18 registries in this dissertation study decreased the population representation by 1%. Data in SEER were not collected from all U.S. states, territories, or protectorates and is limited to 18 participating urban and rural regions across the country (NCI, 2010). Some geographical areas are well represented, whereas other do not have representation. This limitation to the dataset should be noted in findings; however, the data remains representative of acute leukemia in the US and was generalized to the overall population.

The SEER database does not code for additional factors that may influence the access to pathological testing services, including lack of available pathology resources and delays to diagnosis. The rarer forms of acute leukemia in this case series were only reported by larger registry catchment areas and may be attributed to expertise in the area gained through exposure to more infant leukemia and/or may represent local policy on the workup of infant leukemia to WHO defined subgroups, whereas other smaller centers may not have performed exhaustive testing of all presentation specimens. There may have been additional pathology and laboratory medicine tests performed on patients in the case series, but these data were not or could not be transmitted to the SEER registry due to limitations of the database. These missing factors may have affected the classification of patients in this case series and/or have suggested further subgroups had the information been deposited into the registry, which may have limited the conclusions of this dissertation study and the application to the infant acute leukemia population. Additionally, limitations were expected regarding appropriate diagnostic tests ordered and subsequent results that are required. Given acute leukemia is a rare disease, a small number of children may not be given appropriate medical attention, and this limitation may have led to the

exclusion of otherwise eligible medical records. Although the SEER population area is comparable to the U.S. population with regard to poverty and education, there tends to be a higher portion of foreign-born persons in the registry. This finding could affect access to treatment based on barriers to health care experienced based on language barriers. Samples in the SEER data are more likely to derive from urban rather than rural areas due to the coverage area of SEER registry regions, which may result in a selection bias related to the area, socioeconomic status, and treatment access of patients deposited in the database (Lau et al., 2015).

Delimitations

Acute leukemia diagnoses during 2008 to 2014 were accessed from the SEER 18 and refined for this dissertation study. The case series included infants diagnosed with acute leukemia within the first 12 months of life. The congenital group was defined as diagnosis within the first 2 months of life, meaning birth to less than 2 months of estimated age at diagnosis, and the infant group was defined as 2 months or more to less than 12 months of estimated age at diagnosis. Each group was divided further for evaluation of differences based on estimated age at diagnosis. Children with diagnoses aged 12 months or more were not included as their leukemia subtype likely represents pediatric leukemia. Adults were not included in this dissertation study as they were not the target population under evaluation. Children with morphological confirmation of leukemia via ICD-O-3/WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 2008 (revised 2017) standards were required to ensure the disease under evaluation in this dissertation study was leukemia. Children without morphological confirmation of disease were excluded, which may preclude otherwise eligible patients from this dissertation study.

Theories

Scientific nosology theory. The desire for diagnosticians to classify disease from broad, widely applicable to fully defined groups is rooted in scientific nosology theory. The ultimate goal of scientific nosology as proposed by Sydenham, Francois Boissier de Sauvages, and refined by Foucault suggested that disease classifications must be created in order to enhance patient care. Indeed, medicine cannot provide the best care unless the disease is readily identifiable, the natural disease is understood, and an intervention exists (Hucklenbroich, 2014; Libby, 1922; Shershow, 1978). As the previous editions of the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues* emerged, there were distinctive changes based on the integration of molecular conceptions of the human genome that replaced older outdated disease pathology groups that had been established based on the flawed existing nosological system in previous versions of the WHO. The 2017 WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues* relies heavily on the genetic testing to generate specific subgroups of acute leukemia, a disease ontology that grew from the early catalogs of human genetic diseases, which ensured disease classifications began to include descriptions of detectable and yet to be detected underlying genetic abnormalities known to drive the disease (Hogan, 2013; McKusick, 1966).

Sadly, for infant leukemia, pathology and laboratory medicine has not achieved this aim of scientific nosology-based classification as of yet as confirmed by the investigator of this dissertation study. This investigator applied scientific nosology to infant acute leukemia, a group loosely defined by congenital and infant forms based on patient age using the WHO 2017 classifications. This combination of pathology and laboratory medicine findings with clinic practices using a retrospective case series has produced medical knowledge necessary for further disease classification. Previously, infant acute leukemia might include the diagnoses of children

from birth to less than 24 months of age with innumerous age stratification groups of the congenital forms ranging from 2 weeks to 12 weeks of age. “Objectively determinable pathological conditions” have emerged as termed by Hucklenbroich (2014) that are necessary to delineate congenital leukemia as a single group of infants from birth to less than 2 months of age and from infants 2 months or more to less than 12 months of age. Furthermore, the application of scientific nosology theory to this group has generated eight diverse age and lineage stratified leukemia groups. The lineage groups, ALL, AML, ALAL, and OAL, were readily divided into two smaller groups based on patient age at diagnoses and congenital or infant leukemia.

AML was more likely in males, and it was diagnosed either very early in life (birth) or very close to the 12 months of age, included more non-Hispanic Caucasian infants than any other ethnicity and race, and was most likely (90%) designated AML not otherwise specified in the WHO 2017 classification. However, the other WHO 2017 subtypes observed in A-AML were acute monoblastic and monocytic leukemia, acute megakaryoblastic leukemia, and acute myelomonocytic leukemia. C-AML was more likely than I-AML to be further categorized by WHO 2017 using a genetic laboratory test, a factor that is critical to appropriate classification from other leukemia subtypes, given they often present urgently to the emergency department or clinic.

ALL was more likely in males, is rare in the congenital form, and is most likely diagnosed in older infants. There were more I-AML than C-AML diagnoses; more Hispanic Caucasian infants than any other ethnicity and race; and most likely (77.3%) designated B-lymphoblastic and leukemia/lymphoma, NOS, in the WHO 2017 classification. However, the only other recurrent WHO 2017 subtype observed in A-ALL was “B-lymphoblastic and leukemia/lymphoma with t(v;11q23.3); *KMT2A rearranged*,” which accounted for

approximately 10% of ALL diagnoses. I-ALL was more likely than C-ALL to be further categorized by WHO 2017 using a genetic laboratory test, a factor that is critical to appropriate classification from other leukemia subtypes given they often present urgently to the emergency department or clinic.

ALAL was more likely in males, is rare in the congenital form, and is most likely diagnosed in older infants. ALAL included more non-Hispanic Caucasian infants than any other ethnicity and race and was most likely (90%) designated mixed phenotype acute leukemia, B/myeloid, NOS, in the WHO 2017 classification. However, the other WHO 2017 subtypes observed in A-ALAL were acute undifferentiated leukemia and mixed phenotype acute leukemia with "t(v;11q23); *KMT2A*(MLL) rearranged." Given the small number of C-ALAL and I-ALAL further categorized by WHO 2017 using a genetic laboratory test may not subdivide infant ALAL further in routine diagnostics; however, testing is and should remain routinely performed given cryptic genetic changes, a finding that is critical to understanding how appropriate classification of ALAL can occur, given they often present urgently to the emergency department or clinic.

Inverse of the other three groups, OAL was more likely in females; is rare in older infants; is more likely in the congenital form similar to AML; included more Hispanic Caucasian infants than any other ethnicity and race; and were all designated acute leukemia, NOS, in the WHO 2017 classification. As all OAL failed by definition to be further categorized by WHO 2017 subgroups using a genetic laboratory test, the group is reserved for the rarest forms of leukemia, and it is critical to understand appropriate classification is a lack of characteristics present in the specimen from other leukemia subtypes, given they often present urgently to the emergency department or clinic.

The scientific nosology theory has driven research focused on the integration of descriptive pathology and clinical data of infant acute leukemia, documented etiologies, and described the

pathogenesis and outcomes of the congenital and infant acute leukemia groups, which has led to the revision of disease categorization presented herein. These emerging classifications form the basis for further research necessary to confirm these classifications of infant acute leukemia.

Sufficient-Component cause model. To classify disease, the medical community must first amass a compendium of disease-causing factors with great care to separate causative from collective or co-morbid factors in the medical literature. The desire to establish the conditions necessary for disease development is parament to disease recognition at patient presentation and is rooted in the sufficient-component cause model (Aschengrau & Seage, 2014; Rothman et al., 2008). The SCCM was applied to this case series and was used for a framework for studies of epidemiology-based causes of diseases in the infant acute leukemia group.

For infant leukemia, pathology and laboratory medicine has not achieved this aim of a complete understanding of the causation in disease development as confirmed by the investigator of this dissertation study. This dissertation study involved the application of SCCM to the infant acute leukemia case series to demonstrate a minimal set of factors and circumstances that when presented will inevitably result in the disease process in young children. This combination of pathology and laboratory medicine findings with clinic practices using a retrospective case series has produced medical knowledge necessary to identify a number of "component causes," but does not present a "complete causal mechanism." Although this dissertation study has made a contribution to the evolution of an infant acute leukemia SCCM, it comes as no surprise this dissertation study of a small case series using retrospective pathology reports has failed to identify a complete causal mechanism, given investigations about this rare entity have been ongoing since its discovery in the late 1800s. Instead, the application of SCCM has driven this dissertation study research that was focused on the identification of additional component causes,

inhibitive events, disease symptoms, and clinical presentation of the disease, which has led to the revision of age-based lineage specific categorization presented herein. These causes differ in age-based lineage specific groups but form the basis for further research necessary to confirm these components are critical to the model development of infant acute leukemia.

Molecular pathology epidemiology. Through the combination of biomedical, epidemiologic, pathologic, and health status, MPE has recently emerged as a research discipline that can evaluate these factors in context of clinical outcome data (Ogino et al., 2016; Ogino & Stampfer, 2010). Traditional epidemiology and pathology research disciplines were segmented and failed to evaluate how interplay between exposure to causative factors, identified risk factors, and the molecular pathology events necessary for tumor initiation or progression generated the malignant state and influenced carcinogenesis, but MPE evaluations can generate a synergy of these disciplines through integration of numerous laboratory medicine diagnostic findings.

For infant leukemia, pathology and laboratory medicine research have never before applied MPE to understand the distinct pathogenic processes aimed at evolving the precision medicine framework for these children. In this dissertation study, Integrative Molecular Pathological Epidemiology Comparative Effectiveness Research generated unique congenital and infant leukemia groups based on epidemiology, demographic characteristics, and pathologic characteristics to generate lineage age stratified subgroups of AML, ALL, ALAL, and OAL as discussed herein (Ogino et al., 2012; Ogino et al., 2016; Ogino & Stampfer, 2010).

This investigator advanced precision medicine for infant acute leukemia using MPE as it documents the simultaneous role of molecular, pathologic, and epidemiologic factors into disease subgroups using a retrospective case series (Ogino et al., 2012). In this dissertation study,

I-MPE-CER was used for the appropriate subgrouping of patients based on disease similarities to maximize efficacy and effectiveness in pediatric hematology-oncology diagnostics and public health policy for clinical care as discussed further in recommendations within this chapter (Ogino et al., 2016; Ogino & Stampfer, 2010).

Social ecology theory. A comprehensive understanding of the clinical outcomes in young infants with acute leukemia relies on the relationships between the social, institutional, and cultural contexts of individual-environment interactions for the health care outcomes rooted in the social ecology theory (Binder et al., 1975; Stokols, 1996). Through an evaluation of the possible barriers to the diagnosis and treatments of disease, such as access to care and their influence of the outcome based on mortality, the application of SET to infants with acute leukemia, the influence of the socio-economic status, and the generated physical and social environments on health care outcomes were evaluated in this dissertation study. These factors included characteristics of the SEER areas by poverty level, unemployment status, family income, number of foreign-born individuals, and incidence of acute leukemia in the infant population in the area. In this case series, there were unique trends in the geographical location of the leukemia lineage age groups and SEER registry, accessibility to care based on insurance status, and treatments administered for age stratified groups that may have influenced health with the same power as genetic heritage and may have resulted in increased risk for the initial leukemia development (Stokols, 1992). There were numerous differences in the socio-economic factors that influence the clinical presentation and disease course of congenital and infant leukemia in the US in children less than 12 months of age, including differences in insurance type, but with most infants with insurance coverage, geospatial limitations in some SEER registry areas and income differences may have affected patient outcomes. There were no

specific geographical areas where social economic factors may have influenced the ability for patients to gain access to additional therapies needed to increase survival outcomes for infants with leukemia, given all patients were documented to be treated with similar if not identical chemotherapy regimens per international guidelines. However, specific leukemia lineage age stratified groups with poor outcome data may require modifications to current standards of care, including the application of more aggressive therapies as a first line treatment or the need to establish further research studies with the aim to generate new more effective treatments for these infants.

In addition, based on the data presented in this dissertation study, clinical algorithms may include altering laboratory testing methodologies based on the patient's demographics documented at diagnosis. Precision medicine-based diagnostics based on documented demographics of the infant leukemia population via adjustments to laboratory testing might include the supposition that an infant presenting emergently less than 2 months of age with an acute leukemia is most likely an AML rather than ALL, allowing for simultaneous rather than subsequent testing for this disease subgroup in pathology laboratories. The outcomes of this infant leukemia case series will influence how diagnostic techniques and treatment modalities are updated to ensure interventions in pediatric hematology oncology are appropriately targeted for maximum impact to patient care.

Implementation science in laboratory medicine. The development of diagnostic tests that have a critical role in the recognition of infant lineage age groups have unquantifiable value and impact to patient care; however, they must be implemented with sound rationale in the clinical laboratory. These laboratory medicine and pathology modalities are integral to many clinical decisions but must be clinically valid with known clinical and cost effectiveness

(Horvath, 2013; Kaul et al., 2017; Khoury et al., 2017; The Lewin Group, 2008). The use of implementation science in this dissertation study indicated diagnostic tests currently used in pediatric hematology-oncology, including morphology, immunophenotyping, and cytogenomic testing, must continue. However, tests should be appropriately stratified based on the likely disease forms in the infant population, such as more I-ALL, followed by I-AML with the two groups combined accounting for 80% of cases of infant in this case series; the lineage groups with the least classification data, OAL and ALAL, and those occurring in the youngest infants (congenital groups combined) accounted for the remaining 20% of cases. Laboratories should be prepared to implement robust testing strategies based on the findings of these diagnostic groups.

The findings of this case series indicated there are currently highly accurate diagnostic and prognostic tests that can be used for clinical decisions in the workup of a suspected infant acute leukemia. However, the implementation of evidence-based laboratory medicine (EBLM) into the clinical management of infant acute leukemia patients must have consideration for the rare nature of this leukemia as confirmed by this dissertation study. Therefore, standard laboratory investigations outlined in laboratory SOPs should combine with physician clinical expertise or lack thereof, given that most physicians will never diagnose this rare entity, include the consideration of the need of the pathologist and laboratory medicine professionals in the request of the most appropriate testing modalities, include an expectation that all cases will be diagnosed effectively, and understand the concerns of the individual patient and families regarding the need for accurate results of such testing (Horvath, 2013). Appropriate application of the findings of this dissertation study fulfill the requirement that laboratory professionals use only the most advanced, efficacious, and effective tests to provide the greatest benefit to the patients. These revisions of laboratory test repertoires for only the infant population may be a

daunting and challenging task inhibited by the rare nature of the disease in the general laboratory; however, large reference laboratories and those of specialty children's hospitals likely provide and are expected to provide an appropriate all-inclusive diagnostic service. However, all infants and their families deserve equitable access to laboratory services, and those clinicians, pathologists, and laboratory scientists must contribute to the appropriate utilization of medical tests through an evaluation of current tests available for a patient at a given site and the timely send out of specimens when warranted to ensure patients are diagnosed appropriately if testing cannot be provided locally for this rare entity.

Recommendations

The SEER registry is invaluable resource for the review of pathology records across the United States. However, it has limitations in the evaluation of pathology records for genetic studies. Although the registry includes WHO defined entities, those cases outside of these parameters may be missing data in the SEER database, may be absent from the database due to the inability to code the data correctly, and/or may be present with limited diagnostic information to appropriately stratify the infant diagnoses. As the SEER registry remains a source of national cancer data, the system must be updated to included many of the advances in precision medicine, including entry of incalculable genetic findings from not just cytogenomic and suggested molecular genetic tests but also experimental or newly emerging test strategies that will allow the system to be used for more appropriate stratification of patients with MPE factors. These updates to SEER must include input fields outside of WHO designated genetic findings, which will become increasingly important as molecular genetic testing becomes a standard of care in the clinical laboratory. Retrospective case series are critical to the evaluation of rare diseases, given the struggle to access a large enough population, but SEER must include all laboratory medicine

and pathology evaluations for a patient population, not only those deemed previously necessary for classification. Without this flexibility, there is a limited ability to utilize the registry to assess for new or emerging disease markers.

Indeed, other databases have become active in attempting to address some of the pitfalls of the NCI SEER database, including the NCI's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program. The TARGET program has been initiated to generate comprehensive molecular characterization of childhood cancers. These data are made readily accessible to the research community to identify therapeutic targets and prognostic markers. However, although TARGET includes pediatric cases that can be stratified to included only infants, there is limited data stored for pathology and epidemiology characteristics, such as that in SEER, but the database does include exhaustive molecular evaluations likely performed in the cohorts. However, a synergy of pathology records similar to the SEER registry and TARGET initiatives may serve to provide an excellent cohort for further studies of infant acute leukemia.

Summary

Why is the study of acute leukemia in young infants necessary? The understanding of the differences between congenital and infant leukemia is unclear, the infant groups are often grouped together with older children, and the population is understudied in the medical literature. Only through understanding of the differences in this population can we appropriately recognize, classify, and treat infants.

As discussed previously, since the discovery of acute leukemia in young infants approximately 115 years ago, confusion has remained regarding the presentation and natural course of the disease. The study of acute leukemia in children has come a long way since Dr.

Frank S. Churchill at the University of Chicago announced in 1904 “the course [of leukemia] differs from the adult type in only minor details” (Churchill, 1904, p. 582). Now, there is understanding that this suggestion to be absolutely false: Childhood leukemia is a distinctive disease with major differences from the disease in adults. However, the promises held and the challenges faced by doctors at the turn of the 20th century that the disease in infants would eventually become easily recognizable by all given newly emerging “blood examination techniques of the time” continues to plague pediatric hematology-oncology (Churchill, 1904, p. 563). It is critical for laboratory medicine and pathology professionals to understand the history of acute leukemia diagnoses and use previous diagnoses to influence current practices in the laboratory. Previous data for congenital and infant leukemia are limited to a small number of studies. There was confusion over congenital and infant leukemia as they were rarely recognized previously, had overlapping pathologies with other diseases, and were even debated as non-distinct entities from adult leukemia. Many of the early studies of the presentation and natural course of congenital and infant leukemia were drawn from few studies from 1900 to 1950, prior to the advancement of early blood component identification technologies (Churchill, 1904; Holsclaw, 1918; Koch, 1922; Smith, 1921; Stransky, 1925). In 1951, Bernhard et al. (1951) combined cases from the United States Armed Forces Institute of Pathology with previous reports and indicated at that time there were more inappropriate reports of leukemia within infants from 1920 to 1950 than accurately classified cases. Furthermore, Bernhard et al. (1951) suggested that pathologists’ keen awareness of the “extraordinary lability” of the infant hematopoietic system combined with the few well authenticated cases in the medical literature had created a paradoxical state of study with fewer cases recognized at the time than in the past 50 years of routine diagnostics (p. 990). However, by 1955 to 1959, infant leukemia began to

emerge as a disease that initiated and existed during intra-uterine life, which stimulated critical research on infant leukemia, and was soon joined with the spur in genetics studies, disciplines that were both desperately searching for the risks associated with disease development before life. Since this time, a number of pathologic characteristics, including genetic abnormalities, have been identified in infant leukemia, but a newly emerged interest in infant leukemia has burgeoned alongside the precision medicine initiative, which may finally provide insight into all changes necessary for malignant transformation in young children. However, there has remained a gap in the medical literature that provided evidence that childhood leukemias required additional study that could evolve the classification of pediatric cancers (Cao et al., 2016; NCI, 2013). The study of infant leukemia has developed tremendously over the years as childhood diseases have emerged as discrete diseases due to etiologic differences and genomic variations with a unique presentation from that of adults.

Recent estimates have suggested approximately 20% of pediatric leukemia lack previously documented characteristics for risk group calculation, and nearly 60% of cases cannot be stratified by known markers for prognosis, but through application of the precision medicine framework inclusive of the unique disease principle, research can and will enhance the ability to recognize the disease. However, as the unique disease principal presents theories that each individual undergoes distinct pathogenic processes, including genetic and epigenetic changes, cellular interplay, and external exposures, and is compounded by influential factors of diet, environment, microbes, and lifestyle, great challenges in the search to uncover the factors associated with the development of acute leukemia in infants are created. Access to previous case reports is paramount to understanding the disease course, and the focus of this dissertation

study was on such a retrospective case series to address the lack of previously documented characteristics.

Given the current knowledge of congenital and infant leukemia, the characteristic changes present in the youngest of children have only just begun to be unraveled. By uncovering the demographics, pathology, and natural course of the disease, the impacts to the development of new treatment modalities are becoming apparent. How to recognize, diagnose, and treat both congenital and infant leukemia are changing. A shift in the laboratory medicine algorithms can address how and when new acute leukemia in children under 12 months of age is evaluated. Precision medicine research efforts focused on improving the outcomes in the youngest of children will require updates to health policy, standard operating procedures in laboratory investigations, and treatment algorithms, but they hold the greatest promise to cure these children.

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Appendix A

IRB Approval

NSU NOVA SOUTHEASTERN UNIVERSITY
Institutional Review Board

MEMORANDUM

To: **Heather Williams**

From: **Rose M Colon, PhD,**
Center Representative, Institutional Review Board

Date: **May 14, 2018**

Re: **IRB #: 2018-259; Title, "The Integrative Molecular Pathological Epidemiology of Congenital and Infant Acute Leukemia"**

I have reviewed the above-referenced research protocol at the center level. Based on the information provided, I have determined that this study is exempt from further IRB review under **45 CFR 46.101(b) (Exempt Category 4)**. You may proceed with your study as described to the IRB. As principal investigator, you must adhere to the following requirements:

1) CONSENT: If recruitment procedures include consent forms, they must be obtained in such a manner that they are clearly understood by the subjects and the process affords subjects the opportunity to ask questions, obtain detailed answers from those directly involved in the research, and have sufficient time to consider their participation after they have been provided this information. The subjects must be given a copy of the signed consent document, and a copy must be placed in a secure file separate from de-identified participant information. Record of informed consent must be retained for a minimum of three years from the conclusion of the study.

2) ADVERSE EVENTS/UNANTICIPATED PROBLEMS: The principal investigator is required to notify the IRB chair and me (954-262-5369 and Rose M Colon, PhD, respectively) of any adverse reactions or unanticipated events that may develop as a result of this study. Reactions or events may include, but are not limited to, injury, depression as a result of participation in the study, life-threatening situation, death, or loss of confidentiality/anonymity of subject. Approval may be withdrawn if the problem is serious.

3) AMENDMENTS: Any changes in the study (e.g., procedures, number or types of subjects, consent forms, investigators, etc.) must be approved by the IRB prior to implementation. Please be advised that changes in a study may require further review depending on the nature of the change. Please contact me with any questions regarding amendments or changes to your study.

The NSU IRB is in compliance with the requirements for the protection of human subjects prescribed in Part 46 of Title 45 of the Code of Federal Regulations (45 CFR 46) revised June 18, 1991.

Cc: Akiva Turner, PhD, JD, MPH
Rose M Colon, PhD

3301 College Avenue • Fort Lauderdale, Florida 33314-7796
(954) 262-0000 • 800-672-7223, ext. 5369 • Email: *irb@nova.edu* • Web site: www.nova.edu/irb

Appendix B

SEER Contract

Last Name: Williams
SEER ID: 14695-Nov2015
Request Type: Internet Access

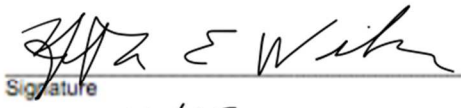
SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS PROGRAM
Data-Use Agreement for the SEER 1973-2013 Research Data File

It is of utmost importance to protect the identities of cancer patients. Every effort has been made to exclude identifying information on individual patients from the computer files. Certain demographic information - such as sex, race, etc. - has been included for research purposes. All research results must be presented or published in a manner that ensures that no individual can be identified. In addition, there must be no attempt either to identify individuals from any computer file or to link with a computer file containing patient identifiers.

In order for the Surveillance, Epidemiology, and End Results Program to provide access to its Research Data File to you, it is necessary that you agree to the following provisions.

1. I will not use - or permit others to use - the data in any way other than for statistical reporting and analysis for research purposes. I must notify the SEER Program if I discover that there has been any other use of the data.
2. I will not present or publish data in which an individual patient can be identified. I will not publish any information on an individual patient, including any information generated on an individual case by the case listing session of SEER*Stat. In addition, I will avoid publication of statistics for very small groups.
3. I will not attempt either to link - or permit others to link - the data with individually identified records in another database.
4. I will not attempt to learn the identity of any patient whose cancer data is contained in the supplied file(s).
5. If I inadvertently discover the identity of any patient, then (a) I will make no use of this knowledge, (b) I will notify the SEER Program of the incident, and (c) I will inform no one else of the discovered identity.
6. I will not either release - or permit others to release - the data - in full or in part - to any person except with the written approval of the SEER Program. In particular, all members of a research team who have access to the data must sign this data-use agreement.
7. I will use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this data-use agreement. If accessing the data from a centralized location on a time sharing computer system or LAN with SEER*Stat or another statistical package, I will not share my logon name or password with any other individuals. I will also not allow any other individuals to use my computer account after I have logged on with my logon name and password.
8. For all software provided by the SEER Program, I will not copy it, distribute it, reverse engineer it, profit from its sale or use, or incorporate it in any other software system.
9. I will cite the source of information in all publications. The appropriate citation is associated with the data file used. (Please see either Suggested Citations on the SEER*Stat Help menu or the Readme.txt associated with the ASCII text version of the SEER data.)

My signature indicates that I agree to comply with the above stated provisions.



Signature

2/2/17

Date

Please print, sign, and date the agreement. Send the form to The SEER Program:

- **By fax to 301-680-9571**
- **Or, e-mail a scanned form to seerfax@imsweb.com**

Appendix C

SEER Data Use Agreement Authorization

Note: This form is primarily applicable to following situations:

1) **you want to access the SEER 1973-2014 Research Data with a named SEER*Stat account;**
2) **a representative of the SEER Program is handing you a SEER 1973-2014 Research Data DVD;**
3) **you are accessing the SEER 1973-2014 Research Data from a shared location such as a LAN.**

SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS PROGRAM

Data-Use Agreement for the 1973-2014 SEER Research Data File

It is of utmost importance to protect the identities of cancer patients. Every effort has been made to exclude identifying information on individual patients from the computer files. Certain demographic information — such as sex, race, etc. — has been included for research purposes. All research results must be presented or published in a manner that ensures that no individual can be identified. In addition, there must be no attempt either to identify individuals from any computer file or to link with a computer file containing patient identifiers.

In order for the Surveillance, Epidemiology, and End Results Program to provide access to its Research Data File to you, it is necessary that you agree to the following provisions.

1) I will not use—or permit others to use—the data in any way other than for statistical reporting and analysis for research purposes. I must notify the SEER Program if I discover that there has been any other use of the data.

2) I will not present or publish data in which an individual patient can be identified. I will not publish any information on an individual patient, including any information generated on an individual case by the case listing session of SEER*Stat. In addition, I will avoid publication of statistics for very small groups.

3) I will not attempt either to link—or permit others to link—the data with individual level records in another database.

4) I will not attempt to learn the identity of any patient whose cancer data is contained in the supplied file(s).

5) If I inadvertently discover the identity of any patient, then
   a) I will make no use of this knowledge,
   b) I will notify the SEER Program of the incident, and
   c) I will inform no one else of the discovered identity.

6) I will not either release—or permit others to release—the data—in full or in part—to any person except with the written approval of the SEER Program. In particular, all members of a research team who have access to the data must sign this data-use agreement.

7) I will use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this data-use agreement. If accessing the data from a centralized location on a time sharing computer system or LAN with SEER*Stat or another statistical package, I will not share my logon name or password with any other individuals. I will also not allow any other individuals to use my computer account after I have logged on with my logon name and password.

8) For all software provided by the SEER Program, I will not copy it, distribute it, reverse engineer it, profit from its sale or use, or incorporate it in any other software system.

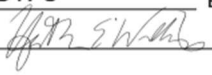
9) I will cite the source of information in all publications. The appropriate citation is associated with the data file used. (Please see either Suggested Citations on the SEER*Stat Help menu or the Readme.txt associated with the ASCII text version of the SEER data.)

My signature indicates that I agree to comply with the above stated provisions. **I understand that this form is not for the purpose of requesting delivery of a DVD by mail.**

First Name: Heather Last Name: Williams

Organization: Nova Southeastern University

Phone: 614-747-3179 E-mail: OSUCat03@gmail.com

Signature:  Date: 26 October 2017

Please print, sign, and date the agreement. Send the form to The SEER Program:

- **By fax to 301-680-9571**
- **Or, e-mail a scanned form to seertrack@imsweb.com**

Saved as http://seer.cancer.gov/dataagreements/seer.pdf

Appendix D

SEER Data Use Agreement for Radiation and Chemotherapy

Data Use Agreement for SEER Radiation Therapy and Chemotherapy Information

November 2016 Data Submission

The population-based Surveillance, Epidemiology, and End Results (SEER) registries collect information on radiation therapy (RT) and chemotherapy given as part of the first course of treatment. RT data are classified by the type of RT received or "no/unknown – no evidence of radiation was found in the medical records examined". Chemotherapy data are categorized as either "yes – patient had chemotherapy" or "no/unknown – no evidence of chemotherapy was found in the medical records examined". These data are available upon request after acknowledging the limitations associated with analyses of the data. Two main limitations affect recommended analyses using the SEER RT and chemotherapy data: 1) the completeness of the variables; and 2) the biases associated with unmeasured reasons for receiving or not receiving RT/chemotherapy. Below we further describe the issues and analyses that could be problematic.

Completeness of the Variables

One recent publication comparing SEER data with SEER-Medicare data reported that overall sensitivity was 80% for SEER RT data and 68% for SEER chemotherapy data. Sensitivity varied by cancer site, stage, and patient characteristics. The overall positive predictive value was high (>85%) for all treatments and cancer sites except chemotherapy for prostate cancer. This analysis used a fairly broad definition for chemotherapy use based on Medicare claims, and further sensitivity analysis is ongoing. [1]

Although sensitivity was moderate, specificity was high, meaning that if RT or chemotherapy was captured in SEER, it was most likely received by the patient. But if it was not captured in SEER, then we do not know whether it was not received by the patient or whether it was missed by the registry. As treatment is increasingly received outside of the hospital setting, there is a diminishing likelihood that it is captured completely. Because we cannot accurately distinguish between "no treatment" and "unknown if patients received treatment," the variables that are released upon request are classified as "yes" or "no/unknown".

Examples of analyses that would NOT be supported by the RT/chemotherapy data, due to the incompleteness of the variable, include:

- Estimates of population prevalence of treatment or patterns of care in the population without appropriate comment on the limitations of the data (e.g., clearly labeling both treatment categories as "yes" and "no/unknown" wherever they appear).
- Estimates of compliance with guidelines
- Comparison of treatment levels in different groups, e.g., investigating health disparities, without adequately stated limitations
- Comparison of outcomes by treatment received

Since we have high confidence that an individual received RT/chemotherapy if the variable is listed as "yes", analyses such as identifying a cohort of patients who received treatment in order to identify risk of adverse events, including risk of second cancers, would be supported by the data.

Biases Associated with Who Receives Treatment

Unlike clinical trials, many factors involved in determining the course of treatment will not be captured in the registry data. Such factors include: patient preferences, physician recommendations, comorbidities, and proximity to treatment providers. Because the data collected do not include these and other factors that are related to why a patient did or did not receive RT/chemotherapy, we do not recommend comparing outcomes conditioned on treatment or comparative effectiveness research using the SEER data without careful consideration of possible biases and appropriate adjustments, potentially using data beyond standard SEER data (e.g. SEER-Medicare linked data). For example, survival differences observed for patients who did vs. did not receive chemotherapy cannot be attributed to the efficacy or effectiveness of treatment without controlling for the factors that determined treatment receipt. Similarly, observed differences cannot be generalized to describe the benefit an individual would expect to receive from chemotherapy treatment.

Reference:

1. Noone AM, Lund JL, Mariotto A, Cronin K, McNeel T, Deapen D, Warren JL. Comparison of SEER Treatment Data with Medicare Claims. Med Care 2014 Mar 15. [Epub ahead of print]

I have read and understand the limitations of the SEER RT and chemotherapy data described above and will include a description of relevant limitations in any analyses published using the SEER data. I acknowledge that the SEER Program has advised me that there are substantive concerns about using these data to address certain research questions as described above. I understand that any findings from such analyses may be inaccurate or misleading.

I will send to NCI any publication that uses SEER RT or chemotherapy variables available through a custom data request. NCI will use this information to track the use of RT and chemotherapy variables collected in SEER.

Print Name Heather E. Williams

SEER*Stat Username/SEER ID williamsh

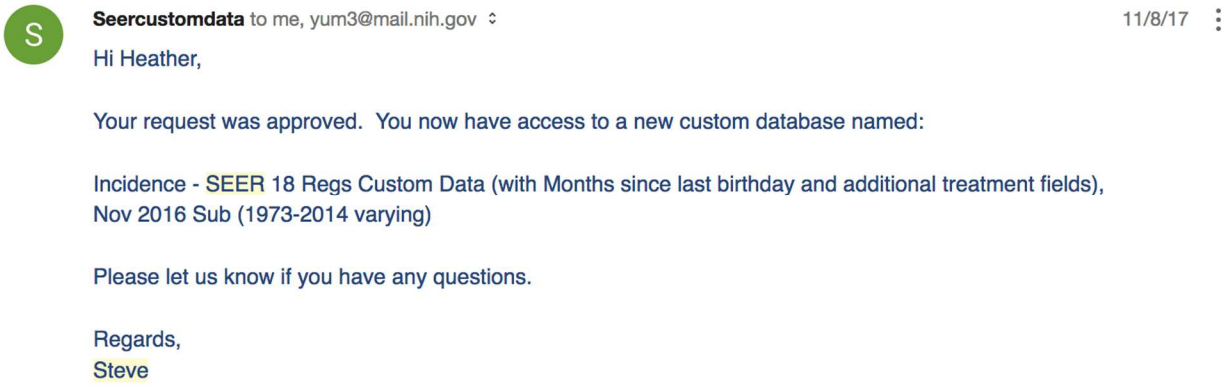
Signature  Date 26 October 2017

Please print, sign, and date the agreement. Send the form to The SEER Program:

- **By fax to 301-680-9571**
- **Or, e-mail a scanned form to seercustomdata@imsweb.com**

Appendix E

SEER Data Use Agreement Authorization Approval



Seercustomdata to me, yum3@mail.nih.gov 11/8/17

Hi Heather,

Your request was approved. You now have access to a new custom database named:

Incidence - SEER 18 Regs Custom Data (with Months since last birthday and additional treatment fields), Nov 2016 Sub (1973-2014 varying)

Please let us know if you have any questions.

Regards,
Steve