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# Leukemia its origin, types, risk factors and survivorship

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## Abstract

Leukemia is a cancer of the body's blood forming tissues such as bone marrow and the lymphatic system. It is most common cancer in the children but mostly occur in adults.The general symptoms in leukemia cancer are appetite and headaches, and red patches on the skin of patients.The hematopoietic stem cell help to regenerate the healthy and leukemia free cells of white blood cells in bone marrow of patients and slowly-slowly cure the leukemia patients. Feline leukemia virus (FeLV) is retrovirus globally impact on the health and cause tumor and bone marrow disorder and immune suppression. The CAR-Natural Killer and CAR-macrophages were introduced as a complement or alternative to CAR-T cells therapy for solid tumor. The thiopurines interfere with the synthesis of nucleic acids in leukemia affected cells in the bone marrow and acting mainly in the S-phase of cell division process in cancerous cells and alloHSCT therapy use to combined targeted therapy and cure to certain types of acute myeloid leukemia which is create by TP53 mutations.The TPMT and NUDT15 genes evaluated their association with 6MP dose intensity and identified 5 and 6 coding variant in TPMT and NUDT15 respectively.

**Keywords:** Leukemia cancer; Feline leukemia virus (FeLV); CAR-Natural Killer and CAR-macrophages; TPMT and NUDT15 genes; Thiopurines.

## 1. Introduction

Blood cells are suspended in plasma which is complex solution containing more than 90% water. The water of the plasma is freely exchangeable with that of body cells and other extracellular fluids to maintain the normal state of hydration of the tissues. Bloods are fluid tissue and plays an important role in the circulation and transport the nutrients, respiratory gases such as oxygen, medicines and carries away carbon dioxide and other waste products from the body [1]. White blood cells play a vital part of your immune system that protects your body rom invasion by bacteria, viruses, fungi, foreign substances and abnormal cells. Generally refers to cancer of the white blood cells (Figure 1).

Leukemia is a cancer of the body's blood forming tissues such as bone marrow and the lymphatic system. It is most common cancer in the children but mostly occur in adults. The cancer usually involves the white blood cells. The white blood cells are potent infection fighters and they are normally grow and divide in an orderly manner according to body needs, but in the leukemia patients, the bone marrow produces an excessive amount of abnormal white blood cells and these new white blood cells mostly produce in the bone marrow do not function properly due to immature development. These immature white blood cells are called blast cells or leukemia cancerous cells [2]. The organization of the malignant clone in Acute Myelogenous Leukemia (AML) has many similarities to normal haematopoiesis with leukemia stem cells (LSCs) that sustain leukemia and give rise to more differentiated cells of blood and these production are interrupted by uncontrolled growth of an abnormal type of cells in bone marrow which affects the ways that the rest cells of the body work [3].

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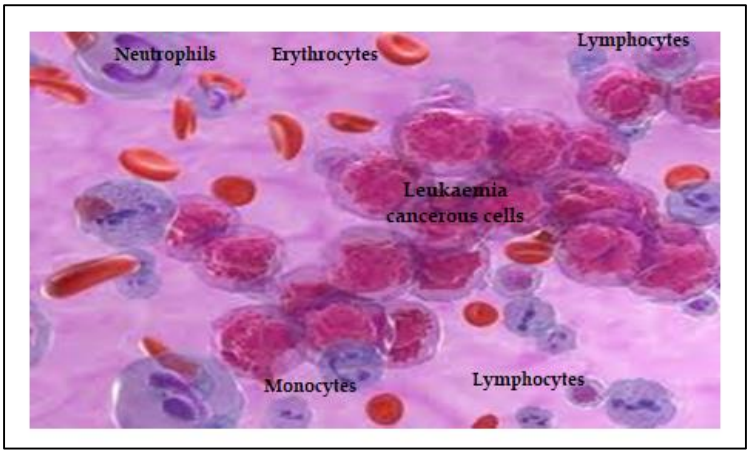


**Figure 1** The smear of blood cells shows the different types of white blood cells and erythrocytes with leukemia cancerous cells which are larger in other cells.

Leukemia Symptoms: Leukemia symptoms commonly includes-

- Fatigue such as tiredness which is not improved by rest, loss of appetite and headaches.
- Infection that are more frequents, weight loss and severe and longer fever with high temperature.
- Swelling in lymph nodes, feeling generally unwell and breathlessness.

There are other general symptoms such as bleeding from nose are more easily and taking place longer times. Redness and red patches on the skin of patients.

In the body physiological organs such as lungs are affected very much and the symptoms in lungs are short and shortness in breath, muscular weakness, bones and joints pain and are tendemless. In the leukemia patients the liver and spleen become enlarge and the skin become purplish patches and spots are seen, and easily bleeding from skin. (Figure 2).

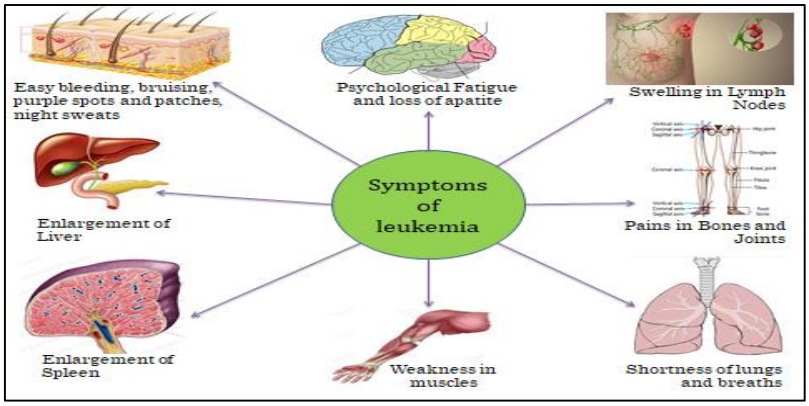


**Figure 2**The general symptoms of leukemia cancer in patient.

## 2. Classification of leukemia cancer

Leukemia classification are used to break the diseases down into four main types-

### 2.1. Acute Lymphocytic Leukemia (ALL)

Acute Lymphocytic leukemia is also called as lymphoblastic leukemia. It is the most common types of the leukemia cancer which is occur in young children mostly but it can also occur in adults. These cancer in the lymphoid cells of the bone marrow and often spread (metastasis) to the blood in other parts of the body such as brain and spinal cords, liver, lymph nodes, spleen and testicles in male patients. The numbers of leukocytes and tumor cells were found in cerebrospinal fluid. Bone marrow biopsy revealed 77% primary atypical blood cells, 89% of which were immature

lymphocytes [4]. Children and adolescents are high-risk group. Approximately 80-85% of cases of leukemia in the pediatric populations are of the lymphocytic subtype [5].

### 2.2. Acute Myelogenous Leukemia (AML)

Acute Myelogenous Leukemia sometimes called acute granulocytes leukemia, acute myelocytic leukemia and acute myeloid leukemia. It is the most common kind of aggressive leukemia in adults and also affects children. The incidence of acute myelogenous leukemia increases progressively with age and induce genetic mutation in children and adolescents [6]. It is a heterogeneous leukemia which creates at gene mutation in the chromosomal rearrangement in hematopoietic precursor through clonal transformation [7]. This type of leukemia starts in the myeloid cells of the bone marrow and spread quickly into the blood. It also spread to central nervous system, liver, lymph nodes and testicles in the male patients.

### 2.3. Chronic Lymphocytic Leukemia (CLL)

It is a slow growing leukemia cancer and mostly affects older persons. The chronic leukemia cancer which is classified as the lymphoproliferative disorder characterized by the relentless accumulation of the mature B-lymphocytes in the bone marrow. It induced immunephenotype-I the peripheral blood, bone marrow, lymph nodes and spleen [8]. By cell signaling, the B-cell receptor stimulate pathogenesis and by interaction between chronic lymphocytic leukemia and other cells such as stromal cells, T-cells and Nurse like cells in the lymph nodes [9].

### 2.4. Chronic Myelogenous Leukemia (CML)

This type of leukemia sometime called chronic myeloid leukemia. It is relatively very rare leukemia and usually appears especially in adults and in some cases older person are also affected [10]. Its symptoms visible after several months and year because of its slow growth. This is generated in bone marrow's myeloid cells. This cancers start proliferation due to disorder by a chromosomal translocation in Bcr-Abl oncogene encoding by kinase activity [11].

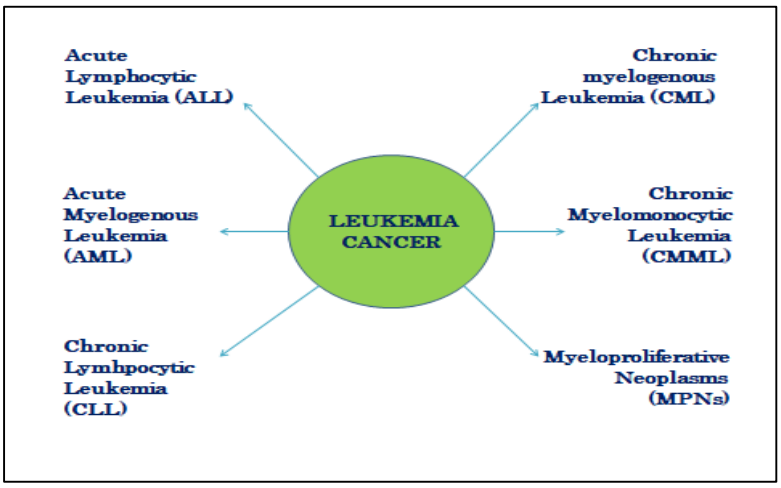


**Figure 3** Classification of leukemia cancer

### 2.5. Chronic Myelomonocytic Leukemia (CMML)

Chronic myelomonocytic Leukemia is a clonal hematopoietic stem cell disorder with myelodysplastic syndromes and myeloproliferative neoplasms. It is inherited leukemia transformation [12]. It is spreading by peripheral blood monocytosis and overlapping between Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs). It induces cytogenetic changes up to 30% in patients and also induces 70-90% molecular abnormalities [13].

### 2.6. Myeloproliferative Neoplasms (MPNs)

This type of leukemia is group of blood disorder and large production of blood is takes place in bone marrow. The hyper viscosity occurs from pathologic elevations of the cellular and cellular proteins fractions of the circulating blood. The triad of bleeding diathesis, visual disturbance and focal neurologic signs are the symptoms of this leukemia [14]. Myeloproliferative disorders emerge in two ways i) as shrinking laboratory abnormalities of seeming unknown consequences and ii) previously diagnosed patients presenting with complications [15] (Figure 3).

## 3. Origin of leukemia cancer in bone marrow

The leukemia stem cells are similar to normal hematopoietic stem cells which are able to give rise to new leukemic cells when transplanted into a recipient, so the normal cells that are able to transform into leukemia cells [3]. There are many factors responsible for starting leukemia cancer in the hematopoietic cells of bone marrow, when any one of the risk factors enter in the body and reach in bone marrow. The leukemia are originate in bone marrow, when affects and growing fast are called acute leukemia and the leukemia which are slow growing called chronic leukemia. These cancers build up in bone marrow and are spread to lymph glands, spleen, liver, lungs, and other parts of the body but without treatment it will be affect and disturb many functions in the body. Although, it is a children's disease but also generate in adults person also (Figure 4).

The bone marrow niche which includes hematopoietic stem cells and their supportive cells interacts with bone marrow and functionally change. These changes closely associated with leukemia progression and suppression of normal hematopoietisis process in bone marrow.

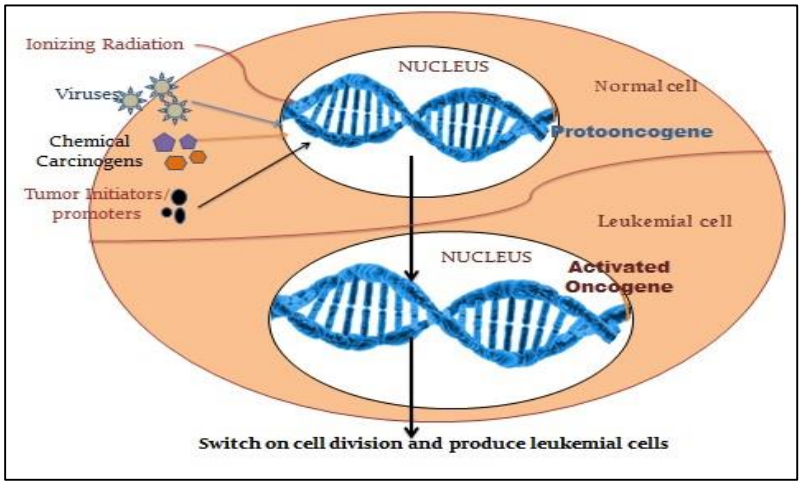


**Figure 4**The action mechanism of the risk factors on white blood cells to switch on the cell division and produce leukemia cells in bone marrow.

The exosomes play an important role in leukemogenesis and progression of disease and organ invasion by the interaction of leukemia derives exosomes and the bone marrow microenvironments [16]. During the leukemia cancer, the exosomes secreted by the leukemia cells and promote the development of leukemia by the influencing and proliferation and apoptosis of leukemia cells. The exosomes also regulate the bone marrow microenvironment and influencing angiogenesis and inhibiting haematopoiesis process [17].

The neoplastic processes can be of B-cells and this classification of B- lymphoblastic neoplasms releases predominantly on genetic and molecular findings [18]. The acute lymphoblastic leukemia (ALL) proliferation of stem cells committed in lymphoid differentiation of B-cells and T-cells [19]. Both types of lymphocytes cells exhibit cytogenetic alterations and many prognostic implications and also associated with acute lymphoblastic leukemia [20].

## 4. Risk factor of leukemia

All risk factors are characterized into following types which are as follows-

### 4.1. Parental Age

The frequent germ line cells mutation associate with aging directly affects the leukemia in children. A higher incidence of childhood cancer among children of older parents. The age of parents might be associated with an increased risk of early childhood cancer in children specially leukemia [21].

### 4.2. Exposure of cancer causing agents

People who exposed to high doses of magnetic field, radon and gamma radiation, explosion of atomic bomb, working in an atomic weapons plants and nuclear reactor plants have the highest risks for the leukemia [22]. If this any types of

exposure can inter in the blood stream, it can induce leukemia cancer. The impacts of drugs, carcinogen chemicals and environmental pollutants progenitors for the hematopoietic stem cells (HSCs) hierarchical manner to the entire myeloid and lymphoid lineages to cause leukemia in bone marrow [23].

Smoking: Smoking cigarettes and tobacco is most important carcinogenic chemical can induces leukemia in blood after interring in the body. Doctors and scientists estimated that about 20-25% leukemia cancer cases are related to smoking [24].

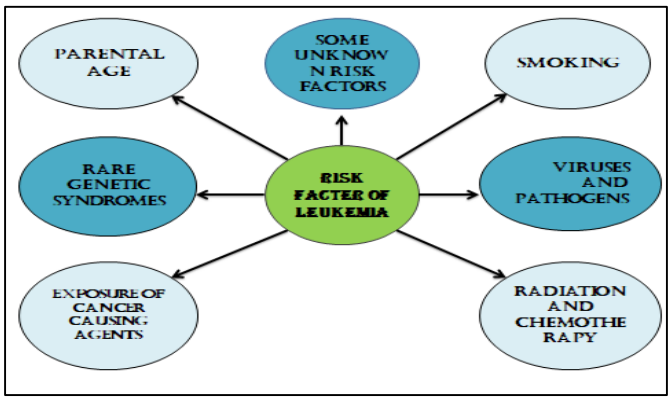


**Figure 5** There are some different risk factors that induce leukemia cancer in bone marrow's haematopoietic stem cells.

### 4.3. Rare Genetic Syndromes

Persons who suffering with any genetic syndrome such as Down syndrome, Fanconi anemia, ataxia-telangiectasia, bloom syndrome are higher risks for leukemia in which about one-third of patients of leukemia suffering with Myelodysplastic syndrome. Some hematologists, clinical scientists and hematopathologists suggest that the acute leukemia and myeloid neoplasms are transmitted from generation to generation [25].

### 4.4. Viruses and Pathogens

Feline leukemia virus (FeLV) is a retro virus globally impact on the health and cause tumor, bone marrow disorder an immune suppression in cats [26] but in human the germ line mutation with myeloid and lymphoid malignancy are cause by the CHEK2 and ATM. [27]. Human Papillomavirus (HPV), Epstein-Barr virus (EBV) Burkit lymphoma, non-Hodgkin lymphoma and nasopharyngeal carcinoma and hairs cell leukemia cancer. This virus also causes HIV suppressed the immune system and enhances the infection of other cancer-causing viruses such as EBV and Herpes virus leading to cancer.

### 4.5. Radiation and Chemotherapy

Radiation and chemotherapy both are the high risks factors for the leukemia cancer. This radiation can cause mutation in white blood forming cells in bone marrow and changes in cell's DNA that later may cause white blood cancer. The sensitivity and the susceptibility to damage of cells towards ionizing radiation are the following orders:

Hematopoitic organs > Reproductive organ > Skin > Bone and teeth > Muscles > Nervous system.

Many people with one or more of these all types' risk factors never develop leukemia but most people develop leukemic in their body with unknown risk factors.

## 5. Treatment in leukemia

Treatment for leukemia depends on many factors which are based on the age and overall health, types of leukemia and their spread to other parts of the body. The common treatments used to fight leukemia includes-

### 5.1. Chemotherapy

Chemotherapy is the major form of treatment for leukemia. New experimental and clinical approaches used to diagnose, monitor and treat this disease hold promise for furthers increased cure rates in the future [28]. Bone marrow

transplantation (BMT) should be applied for the patients a risk in those leukemia such as cytogenetic abnormalities for AML and prognostic factors in ALL. In CML patients the bone marrow transplantation offer only cure but Interferon therapy for CML still a matter of controversy. Interferon and related drugs may be beneficial for CML patients [29] (Figure 6).

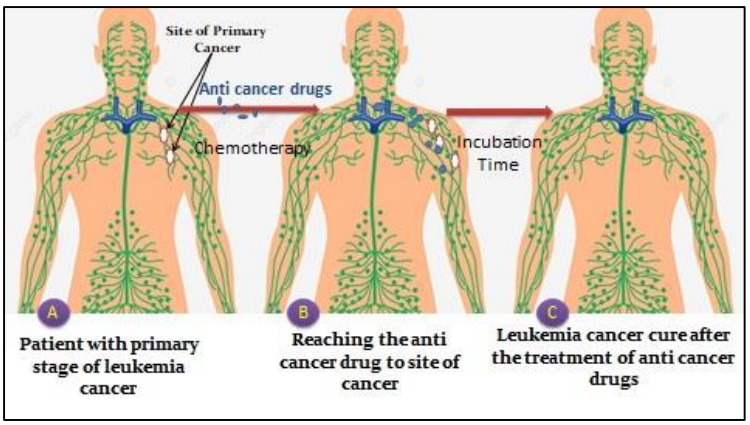


**Figure** 6 By the chemotherapy process, the patient is treated with high dose of anticancer drugs which can treat and cure the patients suffering from leukemia cancer.

### 5.2. Targeted therapy

This therapy based on specific abnormalities and in this treatment blocks abnormalities present in the cancerous cells by killing it. The alloHSCT therapy use to combined targeted therapy and cure to certain types of acute myeloid leukemia such as those with TP53 mutations [30].

### 5.3. Radiation therapy

In radiation therapy X-rays or other high energy beam of light rays are used to kill the leukemia cell in patients to cure the leukemia and stop their growth. In this therapy the patient lie on the table and the X-rays machine moves around the patients and the beam excreted by machine precise the targeted point in the body to cure its growth. Radiation therapy may use to prepare for bone marrow transplantation. Durable control of systemic disease in blood and bone marrow has significantly improved survival but in this method therapeutic challenges play the important role [31].

### 5.4. Bone marrow transplantation

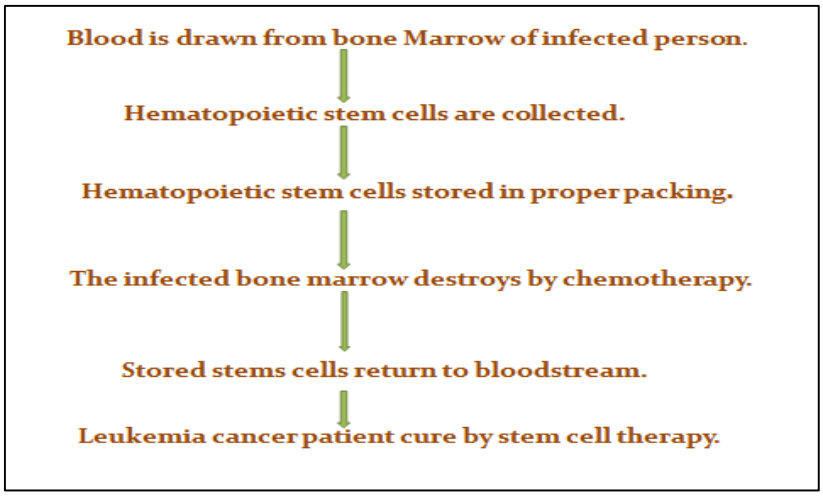


**Figure 7** Autologous Bone marrow transplantation process in Leukemia treatment.

The bone marrow transplant techniques help in the restoration of healthy stem cells by replacement of unhealthy bone marrow cells with leukemia, and regenerate the healthy bone marrow stem cells. This technique is also called as the stem cell transplant. The hematopoietic stem cell help to regenerate the healthy and leukemia free cells of white blood

cells in bone marrow of patients and slowly-slowly cure the leukemia patients. In this technique the patients of leukemia receive high dose of chemotherapy or radiation to kill all leukemia cells in bone marrow and then the patients receive healthy hematopoietic stems cells which help to rebuilds bone marrow cells. The major advantage in the diagnosis, classification and treatment of adult acute leukemia's have resulted in significant increases in the number of complete remissions and long term disease free survivors [28]. Figure 7).

### 5.5. Immunotherapy

Immunotherapy uses your immune system to fight cancer especially leukemia and it is novel immune approaches to leukemia immunotherapy, while promising for specificity and long term protection as single therapy. The molecular and biochemical processes that lead to fight malignant transformation of myeloid and lymphoid cells and leading to long term survival of patients of acute myeloid leukemia and lymphoma cancer [32]. The role of immunotherapy used in the maintenance of remission in children with acute myelogenous leukemia mainly involved adults [33].

### 5.6. Engineering immune cells to fight leukemia

The chimeric antigen receptor (CAR)-T cell therapy has emerged as a promising immunotherapeutic approach to fight cancer. The CAR-Natural Killer and CAR-macrophages were introduced as a complement or alternative to CAR-T cells therapy for solid tumor. This therapy does not require HLA compatibility and has limited toxicity [34]. This therapy works against blood cancer and have potential to fatal toxicity such as in cytokine release syndrome and have high costs are some shortcomings that limit the clinic application of CAR-engineered T lymphocytes. The natural killer (NK) cells are proved to be promising immunotherapeutic candidates for treating cancer and cell line, cord blood, peripheral blood induced pluripotent cell-mediated cytotoxicity (ADCC), as well as the activation of these cells[35] [36].

### 5.7. Clinical trials

It is experiments to test new cancer treatments and new techniques of treatments. In children and adults with acute leukemia is bulk of clinical trials of immunotherapy in children with acute lymphoblastic leukemia have failed to demonstrate a beneficial effects. Immunotherapy trials for acute myelogenous leukemia mainly have involved adults [33].

## *6.* Survivorship in leukemia

Cancer survivorship is a growing public health challenges that is effectively depend on appropriate identification of survivors and their families' specific needs. There are few survivorships in low and middle income countries and more evidence based studies are necessary to develop a comprehensive approach to cancer survivorship [37]. Cancer survivors restrictions on daily living, social eating and financial concerns which survivors an overall high mentally and enjoyment of life included adapting to a new normal and increased involvement in cancer support and faith groups. These included receiving more information about and being more involved in the treatment care plan, referrals to therapy and support groups and more comprehensive follow in survivorship.

The adult patients with myelotoxicity had a normal TPMT genotype and also inaccuracy between genotype and phenotype TPMT activity [38] while, genotyping sensitivity ranged in patient with intermediate and low enzymatic activity [39]. The Thiopurine cytotoxicity based assay altered NUDT15 activity without affecting protein stability. Structural elements to NUDT15 stability of catalytic activities with single amino acid resolution. The functional effects for NUDT15 variants accurately predicted toxicity risk in patients treated with thiopurines with highly sensitive and specificity compare to bioinformatics algorithms and their variant function provide a comprehensive ability to implement pharmacognetics-guided thiopurine treatment individualization [40].

The cure of acute lymphoblastic leukemia (ALL) and germ line variants in drug metabolizing enzyme genes such as TPMT and NUDT15 and Both have linked to the risk of thiopurine toxicity. The TPMT and NUDT15 genes evaluated their association with 6MP dose intensity and identified 5 and 6 coding variant in TPMT and NUDT15 respectively [41]. The thiopurines interfere with the synthesis of nucleic acids a leukemia affected cells in the bone marrows and acting mainly in the S phase of cell division process in cancerous cells. This drug completes with Mercaptopurine, hypoxanthine and guanine for the hypoxanthine-guanylphophoribosyltransferase and is converted to thioinosine monophosphate (TIMP) [42]. According to the above information and data analysis, the development of leukemia survivorship interventions to inform optimal clinical guidelines based on the patients perceived needs [43].

The alpha diversity in the tumor microbiome of LTS patients and identified an intra-tumoral microbiome signature (*Pseudoxanthomonas-Streptomyces-Saccharopolyspora-Bacillus clausii*) highly predictive of long term survivorship in

both discovery and validation. By the process of fecal microbiota transplantation (FMT) from STS, LTS or control donors, the doctors and scientists were able to differentially modulate the tumor microbiome and affects tumor growth as well as tumor immune infiltration [44]. Younger and spousal caregivers have greater unmet have their relative with cancer overwhelming consistently associated with unfulfillment of their need in various domains across the long-term survivorship phases [45].

## 7. Conclusion

According to the finding the contribution of earlier subjective caregiving stress to family caregivers need not being met both currently and years later which in turn related to poorer quality of life across different family caregivershiptrajectors. These finding suggest that identifying at risk subgroups of family caregivers based on demographics and assessing caregiving stress as a priority in psycho-oncology research and clinical practices [45]. Social and cancer control policies in Brazil also provide resources, clinical, psychological and social support for controlling the cancer specially leukemia and breast cancer. Cancer survivors also receive rehabilitation and work reintegration guidelines with broad access to qualified cancer information, development of an integrated patient-centred care and more research resources for the country post treatment cancer period. [37]. Country where resources are limited, the diagnosis and treatment services are initially target all patents presenting with curable cancer such as breast cancer, leukemia, cervical and oral cancer all type of cancer can be detected early including childhood acute lymphatic leukemia which has a high potential cure although it cannot be detected early. All the services need to be provided in an equitable and suitable manner and when more resources become available the programme can be extended to include other curable cancers as well as cancers for which treatment can be prolong survival considerably.

Above all services need to be provided in an equitable and sustained manner and when more resources become available. Other methods are used for curable cancer as well as incurable cancer for which treatment can prolong survival considerably. The world health organization (WHO) wishing to countries to share their success in diagnosis and treatment and welcome request from countries for providing information which are relevant to their specific needs. This qualitative analysis referrals to supportive care services including speech language pathologists, physical therapists and dieticians into the standard of care during the treatment of cancer patients and assists survivors in adopting to life after treatment and managing long term health consequences of their disease.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

None of the authors have a conflict of interest.

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