JESSE & JULIE

RASCH FOUNDATION

HODGKIN'S LYMPHOMA

An Environmental Scan

1.0 INTRODUCTION

1.1 Project Background

This environmental scan titled: *Hodgkin's Lymphoma: An Environmental Scan* prepared for the Rasch Foundation by dmgroup is a broad look at the 'state of affairs' of Hodgkin's Lymphoma with an emphasis on the epidemiology, clinical characteristics and various treatments including: conventional, complementary and alternative therapies. The environmental scan is not an exhaustive presentation of all information available regarding Hodgkin's Lymphoma nor is a systematic literature review; rather the report is designed for all audiences and the Rasch Foundation team to encourage better understanding of Hodgkin's Lymphoma across a variety of areas and specifically for information for use surrounding future activities of the Rasch Foundation in the area of Hodgkin's lymphoma (HL). This project is intended to practically facilitate the Rasch Foundation interest in HL and is comprised of the academic literature, gray literature, pertinent organizations associated with Hodgkin's Lymphoma, funding and granting agencies along with other electronic information sources that all provide an overview of the environment where research, clinical activity, programming and information exists surrounding Hodgkin's Lymphoma.

Following the environmental scan summary, a discourse is presented where gaps in research, resource needs and funding priorities were identified from the academic and gray literature. The project involves two distinct components: 1) the environmental scan that provides an informed understanding of HL with the overarching objective of giving the Rasch Foundation information that will aid in an overall understanding and 2) a resource consisting of a list of selected organizations to consider for either further information or possible collaborating opportunities regarding HL.

The report includes:

I. A summary of an environmental scan comprised of academic literature, gray literature, relevant organizations and electronic information sources

II. Bibliographic Resource

III. A resource of electronic sources and organizations relevant to Hodgkin's Lymphoma

IV. Recommendations and suggestions for consideration surrounding the Rasch Foundations activities regarding Hodgkin's Lymphoma

1.2 State of Affairs: Hodgkin's Lymphoma

Hodgkin's Lymphoma (HL) is a particular type of cancer within the larger group of lymphomas. This cancer develops and affects the immune system, which is responsible for protecting the body from certain diseases and infections. The incidence of HL continues to rise and most often affects younger adults and males and is the most frequently occurring cancer among 15 to 34 year olds in industrial nations (Punnett, Tsang, and Hodgson 2010) .

The etiology of Hodgkin's Lymphoma remains unknown although scientists and clinicians are beginning to understand the role of infectious disease. Importantly, HL is a highly treatable cancer and research is now focused on reducing the morbidity and mortality associated with conventional treatments while also moving forward in developing new less invasive therapies. Issues surrounding nutritional science and alternative treatments require further investigation and understanding to reduce the morbidity and burden of illness for those afflicted with HL. Overall, HL is a highly treatable cancer.

2.0 METHODOLOGY

2.1 Academic and Gray Literature Search: Databases

The academic literature was retrieved from the following databases: PubMed, CINAL, EMABASE, Sociological Abstracts and Scholars Portal Research and numerous electronic sources of information. Identified keywords were used along with other parameters that included years 2004-2010 and English publications only. In instances were sentinel or important articles preceding 2004 were found, they are also included. Appendix A: 'Bibliographic Resource: Report Citations' (located at the end of this document) is a resource list of various references from both the academic and gray literature and citations used in this report.

2.1.1 Strategies and Keywords

In order to examine the state of affairs concerning HL, it was important to use research and clinical terms associated with Hodgkin's Lymphoma. Appendix B: ‘Search Strategy: Keyword Summary’ details the selected key words used in all searches that gathered information contained within this report. Initially, searches were performed using ‘Hodgkin's Lymphoma’ and followed by secondary terms such as ‘lymphoma’ and ‘Hodgkin's disease’. Subsequent searches incorporated tertiary terms e.g., epidemiology, treatment, risk factors etc. The process continued until information was gathered using all the terms listed in Appendix B.

2.2 Websites and Organizations

The electronic information reviewed for the environmental scan used several search engines: Google, Google Scholar, Google Chrome, Mozilla Firefox, Internet Explorer and Safari. For a complete list of organizations and electronic resources see Appendix C: 'Organizations and Electronic Resources: Information and Blogs'.

3.0 FINDINGS FROM THE ENVIRONMENTAL SCAN

3.1 Introduction

The following section of the report provides an overview according to specified topic areas regarding Hodgkin's Lymphoma. Initially, the section begins by defining the classification of the different types of HL followed by a brief presentation of the differences between HL and non-Hodgkin's lymphoma. Next, a discussion of the epidemiology and the various risk factors associated with Hodgkin's Lymphoma and finally a focus on the symptoms diagnosis, prognosis and treatment including conventional, complementary and alternative therapies.

In the broadest sense, cancer occurs in the body when the DNA within a cell results in an abnormality. The changes to normal DNA are from either an inherited condition programmed within the cell or an exposure within the environment (e.g., a carcinogenic) that creates an abnormality. Under normal processes, the body's immune system is able to identify and destroy such abnormal cells; however, when normal processes do not occur, the proliferation of the cancer cells continues in an uncontrollable rate, which over time produces a cancerous tumor. When this occurs within the lymphatic system of the body, it is known as a lymphoma.

The immune system is responsible for ensuring that bacteria and viruses or any foreign entities along with mutations within the body are identified and destroyed, thereby maintaining health. The immune system is composed of various cells, tissue and organs. Within the larger immune system is the lymphatic system, which is integral to overall immune functioning. The lymphatic system is found throughout the body and consists of organs, nodes, tissue and the lymph fluid itself. This fluid is carried throughout the body by a network of tubes and lymph vessels. Lymph nodes, which are found primarily in the neck, under the arms and in the groin area filter the lymph fluid and remove unwanted material such as bacteria, parasites, viruses and toxins.

Specific components of the lymphatic system that recognize and destroy undesirable material in the body are the lymphocytes. Lymphocytes are a particular type of white blood cell

that forms in bone marrow, spleen and lymph nodes. Lymphocytes circulate throughout the body in both the blood and through various lymph vessels. There are two major categories of lymphocytes known as B and T lymphocytes. B lymphocytes mature into plasma and very particular proteins called antibodies. Such antibodies are crucial for immune function as they react with specific types of invaders. In other cases, where the undesirable cell is formed within the body's own cells and can avoid detection by the B lymphocytes, the T-lymphocytes are able to identify situations where the body's own cells pose a risk and the T-lymphocytes take over to destroy abnormalities directly. Specifically, T-lymphocytes attack viral invaders and destroy abnormal cells of which cancer cells are one type (see Appendix D: The Lymphatic System) for a comprehensive look at this system).

When a cancer develops within the lymphatic system it is termed a lymphoma and there are approximately 67 sub-types currently identified. In general, all lymphomas are divided into either Hodgkin's lymphoma or non-Hodgkin's lymphoma. Hodgkin's lymphoma occurs when a lymphocyte (most frequently a B-lymphocyte) becomes abnormal and specifically, the abnormal cell contains Reed-Steenberg (RS) cells along with other types of abnormal and inflammatory cells. Each cancer cell, such as the RS cells express a particular antigen. An antigen is a chemical that is associated with some entity in the body, such as a virus, bacteria or cancer cell that denotes it to the immune system as foreign substance. Normal functioning lymphocytes in the immune system recognize the antigen as an invader to the body and produce an antibody specific to each antigen facilitating the process of identifying and destroying potentially harmful invaders. In the case of classical Hodgkin's lymphoma, the cancer cells continue to divide and grow at a rapid rate overwhelming the immune system's ability to use normal processes to eliminate the cancer cells. Conversely, non-Hodgkin's lymphoma (NHL) is also a cancer found within the lymphatic system; however, most NHL's are B-cell types with diffuse large B-cell and follicular lymphomas being the most common and are indolent or slow growing versus aggressive types of cancer respectively.

3.2 Classification of Hodgkin's Lymphoma

According the World Health Organziation, Hodgkin's lymphoma has 5 sub-types although 4 specific sub-types are referred to as classical Hodgkin's lymphoma (cHL) and one additional sub-type, nodular lymphocyte predominant Hodgkin's disease
(NLPHL) is considered a distinct entity. Within classical Hodgkin's lymphoma the 4 subtypes are: 1) Nodular Sclerosis 2) Mixed Cellularity 3) Lymphocyte Depletion and 4) Lymphocyte-Rich. Classical Hodgkin's lymphoma accounts for over 90% of all cases whereas NLPHL accounts for approximately 5% (A. Engert et al. 2009). (See Appendix E for a summary of characteristics according to classification and subtype). Among the cHL sub-types, the cancer cell itself is referred to as the Reed-Sternberg (RS) cell, which accounts for a very small portion of the cells that form the entire tumor. In the majority of cases, the RS originate from B-cell lymphocytes; however, in approximately 2% of tumors, the RS cell is of T-cell lymphocyte origin.

NLPHL is considered quite different from the classical sub-types based on the clinical characteristics. Furthermore, NLPHL also has different treatment recommendations. The cancer cell found in NLPHL is referred to as the LPHL or L&H.

3.3 Differences Between Hodgkin's and Non-Hodgkin's Lymphomas

There are a few distinct differences between HL and NHL including how the disease spreads, where tumors are most commonly found in the body and variances in symptomology experienced by individuals. Additionally, treatment protocols are very different. HL is not as common as NHL and the age of onset for HL occurs in a bimodal (2 age time points) distribution with the average age of onset at 28 years and a less substantive peak after age 55, whereas it is less common to see cases of NHL in people under age 50 (National Cancer Institute 2007a). For both HL and NHL the most common location of the tumors is in the lymph nodes and occurs above the collarbone (National Cancer Institute 2010).

Specific to HL, malignancies are also found in the chest area, whereas in NHL tumors in

the abdomen are more common. Similarly, in HL as few as 4% of cases demonstrate cancer outside the lymph nodes, which differs significantly in NHL where nearly one quarter of all patients have confirmed lymphoma outside the lymph nodes. In terms of the symptoms of both HL and NHL, they are quite similar; however, approximately 40% of individuals with HL will show symptoms that apply to the whole body or systemic symptoms such as weight loss, night sweats and/or fevers. In NHL systemic symptoms are not as common.

An important difference between both lymphomas surrounds the progression of disease. In HL, the progression is often quite orderly spreading in a downward pattern from the initial site to each lymph node and rarely diagnosed in stage IV. Additionally, when HL first presents below the diaphragm it most frequently progresses to the spleen. Conversely, in NHL nearly 40% of diagnosed cases are at stage IV, which are more likely to spread and not as predictable in terms of their progression.

3.4 Epidemiology

Estimates released in May of 2010 from The Canadian Cancer Society state a total of 930 cases of HL will be diagnosed in Canada this year (Canadian Cancer Society et al. 2010). In 2007, the American Cancer Society referred to HL as an uncommon cancer and reported approximately 8,000 new diagnosed cases (American Cancer Society 2007). However, within all lymphomas; HL is frequently occurring and in the West up to 4 new cases can be expected for every 100,000 (Küppers, Yahalom, and Josting 2006). Epidemiological data consistently demonstrates across all subtypes of HL and in developed countries there is a bimodal or two frequently occurring patterns surrounding the prevalence. One peak in young adults between ages 15 and 34 years and a second peak between ages 55-60 (Adamson and McNally 2005). Specifically, for younger people, it is the most diagnosed cancer in adolescents between 15 and 19 years old (Punnett, Tsang, and Hodgson 2010). This relationship holds across European, Australian, American and Hispanic populations. Concerning individuals of Asian descent, there are fewer cases among younger aged people. Therefore, compared to older adults (over age 40), who have a lower incidence of HL; young people are diagnosed with HL more often (Glaser and Swartz 1990).

More specifically, younger adults tend to develop the HL sub-type, nodular sclerosis more frequently. Furthermore, it has been suggested that the nodular sclerosis sub-type of classical HL is in fact a distinct entity with different epidemiological and other characteristics. This sub-type is more common in females and is less often associated with the Epstein-Barr virus (Mani and Jaffe 2009) whereas among older adults mixed cellularity and lymphocyte depletion sub-types are seen most frequently. In the developing world, there is an absence of the bimodal distribution, there is a peak in boys, lower rates in adults and the most common sub-type is mixed cellularity. Furthermore, in the developing world HL is diagnosed at the advanced stage more often (Aster 2010) (Siddiqui et al. 2006).

Numerous studies conducted globally, for example in India and in North America between 1960 and through the 90's, demonstrated a consistent consensus that the incidence rate of HL increased among both adolescents and young adults with the preponderance of cases attributed to females with the HL sub-type NS. Conversely, studies in the UK and Europe found decreasing cases of HL in all but males between 15 and 24 and no overall change in incidence rates. A 2006 study in the United States examined Cancer Registry data from 1969 to 1998 and found that there were more new cases of HL even when considering how diagnostic techniques may have resulted in finding more new cases and diagnosing such cases earlier in the disease process over time.

3.5 Risk Factors

Overall, the cause of HL is largely unknown and it is important to note that many individuals, who have HL, do not have any associated risk factors. However, research has established a number of risk factors that can increase the likelihood of having the disease and include; demographic characteristics such as age, sex, socio-economic status and ethnicity; medical history including having a relative with HL and other clinical factors such as a compromised immune system and/or particular infections.

One of the most significant negative risk factors associated with HL is being older. Older adults are more likely to have advanced and aggressive disease; they too experience increased

toxicity from treatment, have shorter survival periods and an increased number of deaths related to treatment (Klimm, Diehl, and Andreas Engert 2007). Considering global rates across all sub-types, HL is more common among men. Caucasians are more likely than African Americans or Asians to have HL and Jewish ancestry is modestly associated with an increased risk of developing HL, even after correcting for socioeconomic status (Ariad et al. 2009) (Raemaekers and van der Maazen 2008) (Gutensohn 1982). In particular, HL in young adulthood has been associated with small family size, single family housing, and relatively high maternal education (Pahwa et al. 2009) (Clarke et al. 2005).

Concerning family history and HL, people with a first degree relative with the disease have an increased risk of developing this cancer. In particular, siblings of those with Hodgkin's lymphoma have a higher risk (Paltiel 2008) (Alexander 1990). First-degree relatives of patients with HL are approximately 3 times more likely to develop the disease than the general population. Genetic predisposition appears to be most evident in twins. When one fraternal twin has HL, the other faces approximately a 7 times greater chance of getting the disease and when one identical twin develops HL, the other twin's risk of the disease has been reported to be almost 100 times that of the general population respectively (Mack et al. 1995). In general, the field of genetic research into HL has far to go and there is some evidence to suggest a vulnerability on both chromosomes 2 and 4 may play a role in the development of HL (Paltiel 2008).

Having a compromised immune system or an altered state of the body's immune system such as when an individual has an auto-immune disease (e.g., rheumatoid arthritis, lupus, multiple sclerosis, under- or overactive thyroid). The result of infections such as AIDS or after certain types of transplants are all associated with a higher risk of HL (Punnett, Tsang, and Hodgson 2010) (Grulich et al. 2007) (Zintzaras, Voulgarelis, and Moutsopoulos 2005). Infectious etiology or causes of HL is becoming more understood among researchers and clinicians including how infections such as mononucleosis (IM), Epstein-Barr (EBV), HIV and other viruses are associated with HL.

Interestingly, a study published in 2009 and completed in Denmark reported an association among tonsillectomy, tonsillitis and HL (Vestergaard et al. 2010).The literature has reported an increased risk of HL for individuals with previous IM infections which are caused by

the EBV virus. Recent studies have confirmed the elevated risk, especially among individuals who were infected with IM between the ages of 15 and 34 (Hjalgrim et al. 2000). EBV infects the B-cells and causes an illness known as infectious mononucleosis (sometimes referred to as "mono"). In people with mono, the body's T-cells seek out and kill the infected B-cells. However, if the patient is experiencing a shortage of T-cells, the EBV-infected B-cells are permitted to build up within the bloodstream and increase the risk for genetic mutations that can cause lymphoma. The increased risk remains high for up to 20 years after infection. For many cases of cHL, the large Hodgkin and Reed-Steenberg (HRS) cells are infected with the Epstein-Barr virus (EBV) and EBV is considered a tumor virus in this particular cancer, thus the Epstein-Barr virus (EBV) is strongly associated with HL (Weiss et al. 1989). Despite this, it is important to note that there is no evidence of EBV infection in many HL patients, so the exact role infectious agents and particularly EBV plays in development of the disease remains unclear and requires continued investigation (Böll, Borchmann, and Diehl 2010) (Weiss et al. 1987).

Individuals with HIV or at risk of AIDS have a significant increased risk of HL; however, this relationship does not hold among people with HIV/AIDS in Africa. Furthermore, among intravenous drug users who also have HIV, they too have more of a chance of developing HL. Other viruses such as the herpes virus 6 (HHV-6) have also showed associations with HL but study results are inconclusive (Lacroix et al. 2007).

Numerous human leukocyte antigens (HLA) types have been modestly associated with an increased risk of HL. HLA's are the unique set of proteins, which are present on each individual's cells and permit the immune system to recognize 'self' from 'foreign'. This association is found in both cases of families and 'isolated' individuals. Lack of HLA class II expression has been associated with a poor prognosis, independent of other known prognostic factors (Diepstra et al. 2005). In general, there is a significant familial association of HL but no specific genes explaining this finding are currently identified (Goldin et al. 2005).

Research into the association of many types of individual cancers and socio-economic status (SES) is reported throughout in the literature. Regarding HL, the results are conflicting and knowing if a true relationship exists between SES and HL is difficult to discern. The most

compelling evidence for such a relationship exists among the youngest (both children and young adults) individuals with HL, where those among the higher SES groups were at an increased risk for HL (Alexander et al. 1991). Similar results from Glaser et al., 2002 also showed young adults from higher socioeconomic classes are at even greater risk than their contemporaries from lower socioeconomic classes; this is particularly true of the nodular sclerosis subtype (Glaser et al. 2002). Conversely, among older adults the results are mixed where either no association at all was found or there was a higher risk of HL among lower SES groups. This finding is in line with other research in the area of cancer in general where an increased risk of cancer is associated with lower SES (Cartwright and Watkins 2004).

3.6 Symptomology

A particular challenge in identifying lymphomas is the absence of symptoms, or when symptoms do appear they are common to a number of other ailments. A majority of individuals, who are diagnosed with HL have no symptoms. For those who do, the primary issue is swelling of the lymph nodes that may or may not be painful and most often occurs in the neck region although can also appear in the armpits and groin areas (National Cancer Institute 2007b). Other symptoms are known as systemic, meaning they apply to the whole body such as weight loss, night sweats, decreased energy and a specific pattern of intermittent fevers, which are known as B symptoms. In very few cases, a persistent itching, which gets worse over time is also documented in a select few cases. A final but infrequent sign of HL is pain in the region of the tumor after the consumption of alcohol although the reason for this remains elusive (Punnett, Tsang, and Hodgson 2010) (Lymphoma Research Foundation 2009).

3.7 Diagnosis

Given there is no single diagnostic test to confirm a case of HL, the diagnosis requires a complete physical exam, the consideration of B-symptoms if present and the results of a number of clinical and laboratory tests. The clinical diagnostic work-up includes: a complete physical exam, thorough medical history, a lymph node biopsy, blood tests, imaging testing (Computed Tomography and Positron Emission Tomography scans), both cardiac and pulmonary functioning tests and possibly the examination of a bone marrow sample. The physical exam

allows the physician to identify any lymph nodes that may be swollen along with examining other areas of the body to detect a build-up of fluid, which are most often found in the chest and abdomen areas.

Biopsies are performed by using either a local or general anesthetic and involve extracting a small portion of tissue through a needle or the excision of an entire lymph node. Many clinicians have a preference for a full excision of tissue rather than a needle biopsy as the excision procedure is more apt to harvest enough tissue for a thorough pathological analysis (Punnett, Tsang, and Hodgson 2010). The biopsied tissue is examined by a pathologist, who will examine the tissue for abnormal cells. In the case of HL, the pathologist will identify RS cells along with other abnormal cells present within the tissue sample. The results of a biopsy are crucial not only for an accurate diagnosis but also if a positive identification of HL is found. The pathology results are extremely important in determining the best course of treatment. In some cases, it is preferential that a hematopathologist, which is a pathologist who specializes in lymphoma, also examines the biopsied tissue.

Specific blood tests are performed in order to examine different components of blood, such as red and white blood cells along with platelets to see whether or not the cells are normal and to count the occurrence of the different types of cells contained within the sample. Additionally, results of blood work can also detect whether or not a tumor is impeding liver or kidney function. Finally, a process called immunophenotyping is important to classify the specific sub-type of lymphoma. Each cancer cell has specific molecular markers or antigens on the surface of each cell, examining the antigens aids in specifying the correct tumor type (Küppers, Yahalom, and Josting 2006).

Another important aspect of diagnosing lymphomas is various imaging tests including x-rays and Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) scans. For example, CT scans provide a detailed image and can help deduce how many lymph nodes are involved along with whether or not major organs are affected. The purpose of all imaging techniques in diagnosing HL is to determine the extent or invasiveness of any tumors and to gauge the overall spread of the disease throughout the body. X-rays are used to ascertain whether or not the disease is 'bulky'. Clinically, the term tumor bulk

designates any type of swelling or lump in the body that may or may not be malignant. In terms of HL, an x-ray will allow physicians to determine if the disease is either low or high bulk. A low-bulk tumor is a single mass of tumor tissue that is less than 10 centimeters in diameter whereas one that is larger than 10 cm is referred to as high-bulk or bulky disease (Punnett, Tsang, and Hodgson 2010).

MRI images return similar information to CT scans; however, an MRI is particularly useful to examine the nervous system including the brain and spinal cord, which is important as tumors may interfere with nervous system functions. As with other scans, PET scans are useful in providing detailed information about the stage of the disease and intrical in providing information for specific treatment options and approaches customized to an individual, while also important for gathering information during or after different treatment modalities to gauge how the cancer is responding to treatment. Previously, another scan known as a Gallium scan was used frequently in the diagnosis and treatment of HL. Both the PET and Gallium scans use a radioactive element that collects within a tumor to assist in determining where the tumors are within the body along with whether or not such tumors are responding to treatment. Recently, PET scans have primarily replaced the use of Gallium scans as the PET scan is much more sensitive (Lymphoma Research Foundation 2009).

In addition to x-rays and scans, many individuals undergoing diagnostic tests for HL have both cardiac and pulmonary (heart and lung) assessments. A multi gated acquisition scan (MUGA) allows clinical staff to assess how well a patient's heart ventricles are working. This is very important for individuals who will undergo a particular form of chemotherapy known as ABVD. Each letter in the acronym denotes the first letter for the drug used in that form of combination chemotherapy drugs. For example, the 'A' in ABVD stands for Adriamycin. This drug is known for toxicity that specifically affects the heart. A MUGA scan provides clinicians a base line for cardiac function, along with assessing whether or not chemotherapy is hindering such function (for more information regarding chemotherapy approaches see the Conventional Treatment, section 3.10). Similar to the MUGA scan is the pulmonary function test, which assesses lung function. Again, the B component of ABVD combination chemotherapy, the bleomycin is known to have a toxic effect on the lungs and this test provides both a baseline and on-going information regarding pulmonary function.

The diagnosis of HL is a complex process of taking all the information from the physical exam, medical history and clinical and laboratory tests to a) determine whether or not an individual has HL and if present, b) use the diagnostic test results to inform the best options for treatment. In most cases, many of the diagnostic tests discussed above are repeated throughout the course of treatment (Lymphoma Research Foundation 2009).

3.8 Staging

Once a diagnosis is confirmed, the cancer is evaluated for the stage of the disease. The standard reference to staging for HL comes from the Ann Arbor system with Cotswold modifications. The stage of any cancer represents how much the disease has spread throughout the body. Specifically, the stage is determined based on several factors such as whether or not the lymphoma is on one or both sides of the body and if the cancer has spread to multiple lymph nodes or beyond the nodes into the spleen, bone marrow or other organs. For HL, there are 4 stages represented by the Roman numerals I, II, III and IV. The stage of HL is helpful in predicting the prognosis or how well the individual is expected to do in treatment, in addition to informing specific treatment approaches. Stage I and II represent less advanced disease and suggests the disease is localized to a limited area. Conversely, stages III and IV represent more advanced or widespread state of HL.

In addition to the Roman numerals, the stage of HL may also have the letters A, B, X or E added. As previously stated, the majority of people present to the physician with no specific symptoms and in that case would have the letter A. For those with symptoms affecting the entire body such as weight loss, fevers or night sweats, they would receive the letter B. The letter, E is also an important piece of the staging information as it indicates the HL has spread from a lymph node into the surrounding tissue and finally X specifies bulky disease. (For more in-depth details of the staging of HL see Appendix F).

3.9 Prognosis and Survival Estimates

The whole purpose of assessing a patient's prognosis is to forecast how well the patient will do in recovering or at least experiencing long periods of remission of the cancer as a result of treatment and other factors. Over the course of diagnostic advancements, effective treatment options and developments in reducing the late effects of standard treatments, Hodgkin's lymphoma is a cancer that has very positive characteristics concerning prognosis. The prognosis is excellent for the majority of individual's with HL.

The individual prognosis a patient is given is an estimate derived from numerous clinical and statistical pieces of information gathered on large groups of patients; therefore, a prognosis is the clinician's best guess of how a particular patient may do in treatment, but the information used to derive a prognosis for a patient is not directly applicable to any one individual and a great deal of variation in how patients fair in treatment is possible.

The International Prognostic Score (IPS) is the standard that is used and specifically has 7 factors that are considered when estimating how an individual will fair through their HL disease process:

- Stage of the disease
- Age
- Sex
- Hemoglobin, Albumin and Lymphocyte levels
- White cell counts

Individuals who receive a diagnosis of HL in later stages, who are older, have bulky tumors (see page 9); multiple lymph nodes affected are all at an increased risk of relapse, resulting in a poorer estimate of prognosis (Lymphoma Research Foundation 2009). Overall, approximately 20% of patients will continue to experience progressive disease and death despite successful treatments for HL (Steidl et al. 2010) (Cuenca, Xhaard, and Mounier 2009). Specifically regarding NLPHL, standard treatments lead to approximately a 95% complete remission (Nogová, Rudiger, and Andreas Engert 2006).

Furthermore, research has focused on additional factors not included in the IPS such as the patient's socio-economic (SES). One hypothesis suggests that access to and the quality of health care may impact overall treatment outcomes (Booth et al. 2010). A 2006 Brazilian study, specifically following patients who had HL for 5 years found a relationship between socio-economic status (SES) and complete remission rate (CR) where individuals with a higher SES had an 85% remission rate compared to 72% among those self-reporting a lower SES (Soares et al. 2007). Other cancer research supports this finding concerning several different types of cancer and the success of treatment. Statistically, 85-95% of patients survive HL especially when the disease is diagnosed and treated early (DeVita and Jose Costa 2010) and Hodgkin's lymphoma has a 5 year survival rate of approximately 90% (Bendall 2010). Additionally, survival rates of individuals with HL differ geographically with Europe having shorter survival rates compared to the United States (Allemani et al. 2006).

3.10 Gold-Standard Treatments: Radiation and Chemotherapy

The information contained within this report regarding treatment is simplified in order to provide an overview of treatment and the basic components involved; however, clinically the various types of chemotherapy agents, exact courses and duration of treatments along with the numerous patients and clinical factors affecting a patient's treatment regime are quite complex. (For additional information including a much deeper presentation of the details surrounding treatment for HL see list of citations at the end of this report).

HL is a treatable cancer for the vast majority of individuals, especially when the diagnosis is made during the early stages and when patients are younger in age. A significant consideration in the treatment of HL is 'late effects' or the consequences for individuals later in life as a result of their initial treatment. The goal is to cure HL completely while at the same time reduce the number of adverse health effects later on as a result of under-going initial treatments (see Late Effects, section 3.11). The specific treatment modality and regime an individual with HL will undergo is a decision based on a number of factors including: the sub-type of HL, the stage of the disease, the rate at which the disease is assessed at progressing, the age of the patient and their overall health status.

Historically, radiation therapy (RT) was used alone to treat early stages of HL; however, as researched evolved, it became evident that wide exposure to radiation contributed significantly to poor health outcomes later in life (Raemaekers and van der Maazen 2008). Involved-field radiation therapy (IFRT) is when radiation treatment is confined to a particular place on the body versus extended field radiation that covers a much larger area. The goal is to confine the radiation treatment to the smallest area possible while ensuring the field includes the cancer cells. As previously discussed, HL tends to progress in a uniform fashion from one lymph node to the next thus, it is possible to predict the pattern and match the radiation respectively. Cancer cells reproduce faster than normal cells in the body and radiation therapy targets these rapidly dividing cells. The radiation damages the DNA or genetic material in the cell that controls cell growth. This allows cancer cells, which are not as adept at repairing themselves to be destroyed.

The amount of radiation used in IFRT, as with all other radiation therapies, is measured in gray (Gy), and varies depending on the type and stage of cancer being treated. Radiation treatments are divided into several small sessions, called fractions. Most treatments with involved field radiation are completed in 4 to 5 weeks. The duration of treatment depends on the dose delivered. IFRT is commonly given after primary chemotherapy treatments; the dose is often based on clinical assessment of how much disease remains. The side effects of radiation depend on the treatment and dose and the part of the body that is treated. During radiation therapy, patients frequently experience extreme fatigue, particularly during that last weeks of treatment. Radiation increases the risk of late effects. Receiving IFRT increases the risk of developing cancer in the organs which were within the radiation field (such as lung, breast, or stomach cancer) 10 or more years after initial treatment (A. Engert et al. 2009).

With the advent of several chemotherapy drugs, a combination of chemotherapy drugs and radiation therapy used together are standard practice. However, randomized controlled trials have failed to demonstrate that the use of combination chemotherapy and radiation is more effective than chemotherapy alone, thus it appears that some individuals, particularly in the very early stages with favorable prognostic factors may in fact be over-treated (Seam et al. 2009).

There are two main reasons for using a combination of chemotherapy drugs, which allow the physician to administer a lower dose of any one particular drug with the goal of reducing the impact of side effects. Side effects from chemotherapy include temporary or permanent infertility, an increased risk of infection, and potential damage to other organs, including the heart or lungs, as well as reversible hair loss. Additionally, using more than one type of chemotherapy drug also reduces the likelihood that an individual under-going chemotherapy will develop a resistance to the drug itself. The most common combination of chemotherapy drugs used for HL is known as ABVD; however there exists variation in the approach to treatment regimes, including specific drug combinations depending on a variety of patient characteristics and clinical factors (Diehl and Fuchs 2007).

According to the European Society of Medical Oncology (ESMO) clinical practice guidelines, classical HL (cHL), when diagnosed at the earliest of stages, a brief course of combination chemotherapy followed by involved-field radiation therapy is recommended (2 cycles of ABVD followed by 30 Gy of IFR). There is on-going discussion of whether or not radiation can be omitted for this group of patients while still realizing the high cure rates. For patients whose disease has progressed beyond early stages but not yet classified as advanced, they are placed into the intermediate group and have the same chemotherapy treatment as early stages albeit 2 additional rounds of chemotherapy. For patients with the most advanced disease, chemotherapy treatment with either ABVD or other combination chemotherapy drugs using up to 8 cycles is recommended followed by 30 Gy of radiation. Similarly, treatment for the sub-type non-lymphocyte predominant Hodgkin's lymphoma, the ESMO guidelines are the same as for cHL with the exception of the early stage, which is treated with radiation alone (A. Engert et al. 2009).

3.11 Biomarkers

The human immune system produces antibodies through the B lymphocytes that are crucial for overall immune function to protect against foreign invaders including: bacteria, viruses, fungi, toxins, parasites and environmental pollution known as antigens. The process

involves the B lymphocytes of the immune system producing a very specific antibody for each antigen and binding to that antigen so that the invader is identified and ultimately destroyed by the immune system. This process happens each time the body is exposed to a new antigen and a memory function exists within the immune system such that after exposure to many invaders, the antibodies provide an on-going protective effect.

Molecular biologists produce certain antibodies such as monoclonal antibodies (MAbs) for the clinical use in diagnosing and treating a number of diseases including lymphomas. Lymphomas are often an excellent type of tumor for this therapy because of the intravascular nature of the tumor, which makes the tumor accessible to drugs given intravenously (Kreitman and Pastan 2006). The objective is to produce enough antibodies to target a particular cell, such as a cancer cell that will interfere with protein synthesis and cause cell death of the cancer cell itself, a process known as apoptosis or 'cell death'. There are currently 2 approved MAbs, rituximab and alemtuzumab. For example, rituximab is used when a patient's own immune system will not produce an anti-body for a particular cancer cell or when a cancer cell does not respond to chemotherapy

The RS cells commonly express the antigen CD30. The CD30 antigen was the first identified on the surface of the RS cell. The specific type of antigen produced is particularly important for targeting therapy. Research is currently focused on developing specific antibodies for new treatments targeted for particular antigens. This type of therapy will allow clinician to target the cancer cell directly and move toward what is referred to as 'personalized therapy'. This will not only target specific cancer cells but is hoped to reduce the effects of treatment caused by more global measures (Böll, Borchmann, and Diehl 2010).

3.12 When Gold-Standard Treatments Fail: Relapse/Refractory HL

Despite the fact that an overwhelming majority of individuals experience excellent treatment and survival outcomes after their initial primary treatment, there remains a group of patients who suffer from two other specific outcomes. One, the relapse of their HL, whereby, the lymphoma returns after a period of time (for cHL the average time is 3 years) or two, those

individuals whose HL becomes refractory or they fail to achieve a complete remission with primary treatment . When either of these situations occurs, secondary or more aggressive therapies such as different forms of combination chemotherapies, also known as 'salvage' chemotherapy and stem cell or bone marrow transplants become further treatment options (Böll, Borchmann, and Diehl 2010).

Individuals who suffer a relapse have a 50% chance of a cure using second-line treatment. However, cure rates are affected by the length of time it takes for a relapse to occur. For those who experience a relapse within 12 months of their initial treatment, cure rates are lower. Those whose relapses occur later tend to have somewhat higher cure rates. The treatment options for patients whose disease has relapsed generally focuses on “salvage” chemotherapy regimens using different combination chemotherapy drugs and in higher doses. In some instances, after high-dose chemotherapy the patient may undergo autologous stem cell transplantation (ASCT) (Gianni et al. 1997). This involves the collection of the patient's own stem cells (before they are destroyed by high-dose chemotherapy or radiation therapy treatments). These stem cells are then reintroduced into the patient's body. High-dose chemotherapy with stem cell transplantation is generally a safe procedure, with less than a 1 to 2% risk of death related to the treatment (Torjman et al. 2007).

3.13 Consequences of Treatments: Late Effects

As a result of their previous cancer treatments, there is a risk of several morbidity issues and death for individuals who have undergone treatment for HL. Further complications are the result of the toxicity of chemotherapy and radiation. An increased risk exists for heart and lung disease, thyroid function problems, sterility and other health issues along with a risk of the development of secondary cancers (Hodgson et al. 2010) (Küppers, Yahalom, and Josting 2006). In fact, among older adults, who were male and particularly among men who underwent ABVD chemotherapy, cardiac complications as a result of the toxicity of treatment is a significant late effect (Myrehaug et al. 2008). A large population study published in 2008 examined mortality rates of patients previously diagnosed and treated for HL compared to the general population between 1967 and 2003. Results showed that there was an increased risk of mortality among the

HL patient group compared to the general public and the progression of HL continued as the leading cause of death. However, over time a clear pattern of decreasing deaths due to infections and toxicity of treatments was noted. Cardiac complications and the appearance of secondary tumors remained among the patient group (Provencio et al. 2008). Although having complications later in life as a result of treatment for Hodgkin's Lymphoma, patients are improving and will continue with the advancement of personalized therapies and targeted treatments to reduce the toxicity of conventional treatments. On-going screening during the post-treatment time periods, such as breast cancer screening for women who have previously undergone chemotherapy or radiation treatments, is essential as are a number of surveillance procedures (Hodgson et al. 2010).

Despite the call from both researchers and clinicians for guidelines surrounding follow-up care for HL patients, there is no consensus and/or uniformly followed guidelines for use. Research suggests that follow-up for HL survivors is poor, too many patients are not followed up with systematic protocols regarding after care (Alfred Ian Lee et al. 2010). For example, there is disagreement about what types of diagnostic/screening tests to use including no consensus around particular imaging technology to use during the follow-up period (Alfred Ian Lee et al. 2010). One such study in the United States found no difference in surveillance of HL survivors using radiography and suggests that CT scans are both cost-effective and adequate with respect to imagine techniques (Alfred Ian Lee et al. 2010). Furthermore there is no protocol for whether or not the oncologist or primary care physician is best suited for on-going surveillance.

3.14 Complementary and Alternative Therapies

Beyond allopathic or conventional treatments for cancer, both complementary and/or alternative therapies (CAM's) are approaches used by cancer patients to seek during the course of their disease. Complementary therapies (CT) are various therapies used in conjunction with standard allopathic care. Conversely, alternative therapies (AT's) are less embraced in Western medicine and are either used in place of conventional treatment, such as when a patient opts out of conventional therapies all together and substitutes AT's in place of conventional medicine, while others turn to AT's when allopathic medicine cannot provide any more treatment options.

There is a great deal of information available regarding CAM's; however, within the medical community consensus surrounding the true effectiveness and the robust nature of the methodology used in examining CAM's is still under debate. In 1998, The Office of Cancer Complimentary and Alternative Medicine (OCCAM) within the National Cancer Institute was formed with the primary objective of providing clinicians and the public with up-to-date information surrounding the research, standardized reporting of the use of CAM's along with information regarding access to such treatment alternatives and adverse events of numerous CAM therapies (Assouline and Miller 2006).

Estimates suggest that between 22% up to as many as 69% of individuals with cancer use complementary therapies for symptom relief from the toxicity of conventional treatment (Assouline and Miller 2006). Among the most common reasons individuals turn to complementary therapies are for cancer-associated pain, anxiety and stress, fatigue along with nausea and vomiting. Specific complementary therapies include: acupuncture, massage, cognitive therapy and art therapy. Alternative therapies such as nutritionally based recommendations, supplements, high-dose vitamin C therapy are alternatives when assessing treatment options beyond conventional therapy approaches. For individuals with Hodgkin's Lymphoma, it is important to note that any product that is labeled 'natural' or 'herbal' may cause serious side effects either on its own or in combination with conventional treatment. Such effects can include liver toxicity and kidney damage among other adverse reactions, especially in combination with chemotherapy treatments.

Despite conflicting results, there is merit in considering certain complementary and alternative therapy options and many individuals with cancer report significant symptom relief and in some cases, the remission or complete disappearance of their disease; however, one must investigate carefully when considering either a complementary or alternative therapy. Ideally, having an individual's health care team work together in order to identify and manage any effects is paramount.

3.14.1 Diet/Nutrition

Of all the current discourse surrounding cancer, diet and particularly nutritional science may in fact be the most complex, controversial yet biologically plausible pathway to treating cancer and importantly preventing cancer. There is intense debate regarding various specific nutritional approaches to preventing and treating cancer. It is clearly beyond the scope of this report to review all the nutritional science; however, it is a notably important body of information and at the very least pertinent to introduce in this discussion. The following section provides an overview of selected approaches to diet, supplements and specific approaches to therapy using naturally occurring substances and nutritional approaches in treating cancer as a whole.

The scientific debate of the effectiveness of many approaches discussed below is the current discourse among many researchers and clinicians. There are a number of methodological, clinical even political issues that impede the development of rigorous scientific investigation and evaluation in the area of diet and nutrition along with other forms of alternative therapy for cancer. Where publications do exist stating the benefits of approaches beyond conventional treatments, there are various other sources refuting their claims. Furthermore, researchers are often caught in the middle of an intense methodological 'rock-and-a-hard-place' situation. In medicine, it is standard research practice that new and emerging therapies designed to fight disease go through a rigorous review prior to any type of wide spread acceptance and approval for use with human patients. Additionally, levels of evidence are clearly outlined and followed, whereby randomized double-blind controlled trials (RCT's) are the 'elite' of all research study designs in medicine and for *good reason*. The methodological practices and scientific conclusions require intense scrutiny. However, some researchers, including Dr. Colin Campbell argue that the RCT is unequivocally the incorrect approach to take with nutrition science as it is over-focused on one entity under examination and associated with one outcome; the RCT is highly suitable to pharmacological studies where one drug is examined for its association regarding one particular outcome; however not well suited for investigations in the area of nutritional science (Campbell 2008a).

Common to alternative therapies is the small-group or case-study whereby individual outcomes and experiences are key to recording what impact treatment had on the patient's health status. Despite numerous positive outcomes experienced by a number of patients using AT's, it is impossible to deem many alternative therapies approaches successful in treating cancer. Scientifically, there are always other factors, mediator variables and issues of methodological approaches surrounding how treatment outcomes were documented to definitively declare such an intervention effective in reducing, eliminating or even preventing a cancer. It is important to remain crystal clear, there are sound principles at play in this debate and such research principles are in place, once again for good reason. However, having said that, it also sets up the situation where alternative therapies are disregarded in cancer therapy. There are researchers, clinicians and individuals with cancer along with survivors, who strongly state the lack of advancement in the development of alternative therapies for cancer is the result of an over-focus on pharmaceutical agents and a lack of endorsement at the research level into not only alternative treatments but the need to recognize, endorse and disseminate numerous studies completed in the area of nutritional science that clearly demonstrate the positive effects diet can have on both preventing and treating cancer (Campbell 2010).

Overall, this does not mean that alternative approaches to the treatment and prevention of cancer do not work; it does mean we cannot make empirical statements using strong evidence to state that they do. This is an important distinction. Because we do not have the scientific evidence to date, based on current clinical research protocols in the peer-reviewed academic journals to declare that alternative therapies can treat or even reverse certain cancers under certain circumstances does not make such interventions ineffective. It does mean we have not shown the success of such interventions successfully using current empirical and methodological requirements in research. There is no way to empirically demonstrate many of these interventions definitively impact cancer; however, there is a plethora of experience on the part of clinicians, researchers and patients to suggest otherwise.

The purpose of this section of the report is to leave the Rasch Foundation with information that is worth considering and possibly investigating in more depth in the future. Despite an inability to declare such interventions empirically relevant, other supporting evidence

from various sources strongly suggests that all have biologically plausible explanations for why and how they can impact the burden of suffering for individuals with cancer. It must be emphasized that very little research to date in this area has focused on HL, particularly in the area of diet. Some preliminary work is underway for Non-Hodgkin's Lymphoma; however, there is a great deal of work to do. Therefore, the discussion below is referring to cancer in general versus any specific type of cancer unless otherwise stated.

3.14.1.1 Controlled Amino Acid Therapy

Since the late 1940's and certainly into the 1960's, the relationship between chemical reactions within the body and the growth of cancer cells has been an area of interest for a select group of researchers. Furthermore, understanding the effect of nutritional components as initiators or catalysts in such reactions is the focus of current clinical investigations. At the National Cancer Institute and the University of Chicago, two physicians, Dr. Rabinowitz and Dr. Lorincz are investigating controlled amino acid therapy (CAAT) and the biochemical effect of such therapy on altering or impairing the DNA synthesis of cancer cells. The CAAT therapy creates a deficiency in the amino-acid availability within the body, virtually eliminating all other sources of protein and reduces carbohydrates, thus inhibiting, even stopping the growth of cancers cells by restricting the availability of crucial protein components a cancer cell must have in order to self-replicate. Additionally, it is well known that cancer cells use glucose almost exclusively to feed on, thus a diet which dramatically reduces carbohydrates sets up a deprivation in the amount of energy available to the cancer cell. Interestingly, the science behind CAAT is the very same approach used in current chemotherapy treatments, the inhibition of DNA and protein synthesis, and interferes with signal transduction receptors on the cellular membrane of cancer cells, thereby impeding their growth (Haddad 2009).

3.14.1.2 Gerson Therapy

During the 1930's, Dr. Max B. Gerson developed a theory in the area of nutritional science based on creating optimum metabolism levels in the body along with detoxifying the liver. Initially, the Gerson therapy was applied to migraine headaches and tuberculosis and in

later years the approach was particularly developed for use in treating cancer. Dr. Gerson hypothesized that cancer tumors resulted from a dysfunction in metabolic processes of the body. Through a specific diet and detoxification regime specifically for cancer, along with re-balancing both sodium and potassium levels, this allows the body to address the errant cancer cells naturally.

An organic diet that includes reducing sodium and increasing potassium levels all work to create normal metabolism through optimal digestion. To achieve this, diet and supplements along with enemas and pancreatic supplements boost the immune system and optimize the body to rid itself of toxins. Once the body rids itself of toxins and returns to homeostasis, diseases such as cancer are dealt with through the body's natural processes, the immune system that detects and destroys cancer cells. Dr. Gerson himself had a number of patients who underwent the Gerson Therapy and experienced positive outcomes in addressing their cancer. Claims by the Gerson Clinic (founded in 1977 by Dr. Gerson's daughter) states among even the most dire cases, where patients were told they had a month to live, the Gerson Therapy increased survival rates and cured a substantial number of patients (The Gerson Institute, 2010).

Clearly noted on the National Institute of Cancer's (NIC) web-site is a statement concerning the review of Dr. Gerson's retrospective studies, chart entries and follow-up notes for over 50 patients using this therapy for cancer. Neither preclinical (human or animal studies) nor clinical trials have demonstrated efficacy of the Gerson Therapy. Additionally, the National Cancer Institute reviewed reports including case studies and anecdotal information. In reviewing the case histories of 6 patients specifically with metastatic cancer, evidence of both physical and psychological benefits were attributed to the Gerson Therapy and the review recommended further examination through a clinical trial investigation. Similarly, the British Columbia, Canada Cancer Agency also states that no data has been made public to support these statements and the American Medical Association has discredited any positive attributes of the Gerson therapy. (For a complete list of Dr. Gerson's publications see Appendix G: List of Publications: Gerson Therapy).

3.14.1.3 Plant-Based Diet

The literature contains numerous studies indicating that a change from the typical Western diet that is high in fat, dairy and processed foods can negatively impact overall health. The nutritional science literature is growing at a rapid rate and there are too many components to review in this report, rather a focus is taken on the work of Dr. Colin Campbell. The Rasch Foundation is currently looking at the nutritional science literature and more detailed information is expected to become available in the near future.

Viewed as the most complete research study along with extensive analysis of diet and lifestyle with respect to disease is the China Study (now specifically referred to as the China Study I). This study focused on nutritional science, included over 300 variables and was conducted in China and Taiwan in more than 2,000 counties. The premise of the study was to examine the diet and other nutritional aspects of this population because of their strikingly lower prevalence of chronic diseases such as heart disease, diabetes and cancer compared to other nations. The vast majority of the population of China and Taiwan adhere to a plant-based diet, although this is expected to change as more influence from the Western world concerning nutrition becomes widespread in these countries.

The consumption of animal protein and in particular high cholesterol levels in China was associated with various forms of cancer including: anal, brain, leukemia and certain cancers of childhood (Campbell 2008b). Conversely, other research studies completed in the Netherlands, which has some of the highest rates of animal consumption in the world, failed to replicate the results found in the China Study. Dr. Campbell emphasizes that this does not necessarily mean there isn't a true association between the intake of animal fat and cancer but that simply reducing the amount ingested may be a necessary factor but not sufficient to impact overall cancer rates. "Only as cholesterol levels drop even further, into the strikingly low levels seen in China, do cancer rates decline" (Campbell 2008b).

Regarding lymphoma, individuals who ate beef, pork or lamb daily compared to those who ate the same foods less than once per week had 2 times the risk of NHL and this was also found among those who consumed other red meats (Campbell 2008c). Similar findings also

applied to those who ingested fats and particularly trans fats, they too had an increased risk of developing lymphoma as did those whose diets were high in fat and especially partially hydrogenated oils (common to fried foods, fast foods, some margarine products and numerous baked goods). In terms of a lower risk of lymphoma, women who consumed 6 or more servings of fruits and vegetables compared to those who ate 3 servings had a 40% lower risk of developing this cancer. The reduced risk of NHL was also found among participants who ate a gluten-free diet and maintained a healthy weight (Campbell 2008c).

3.14.2. High-Dose Vitamin C Therapy

The use of vitamin C therapy is an area of interest to researchers. As far back as the early 1950's, vitamin C was hypothesized to prevent the spread or metastases of cancer and later Scottish investigators sought to demonstrate how vitamin C added to the survival of patients with advanced cancer. However, by the early 1980's, two separate clinical trials failed to demonstrate any therapeutic effects of vitamin C therapy and there was significant criticism of more recent trials performed at the Mayo Clinic, which specifically used oral vitamin C and failed to show any significant effects (National Cancer Institute 2009).

In February 2010, researchers in the United States reported the successful use of vitamin C therapy to suppress both the growth and spread of tumors surrounding prostate cancer in rats (HARVEY B. Pollard et al. 2010). Also, animal studies at the National Institute of Health and University of Kansas have demonstrated that tumor size and spread were reduced in mice who received injections of vitamin C among ovarian, pancreatic and giloblastoma tumors (National Cancer Institute 2009). At issue is the lack of pre-clinical and clinical research examining the effects of this treatment while also simultaneously examining dose responses, methods of the delivery of vitamin C, specific types of vitamin C (ascorbic acid and dehydroascorbic acid) and which particular tumors are possibly susceptible to treatment. Furthermore, controlling for the effects the patient may be receiving from conventional therapy or any other CAM therapies in use while undergoing vitamin C therapy is necessary to improve the rigor of studies (Assouline and Miller 2006).

The premise of high-dose vitamin C is based on increasing the level of antioxidants (vitamins C, A and E along with others) and effectively reducing the amount of free radicals in the body. Free radicals accumulate because of exposure to toxicity, for example toxins in the environment such as cigarette smoking. An oxidation effect occurs, whereby free radicals (also known as reactive oxygen species) increase and cause damage to particular molecules which in turn compromises otherwise healthy tissue and cells. There is recent scientific evidence which suggests that vitamin C reduces oxidative stress within the body and may be cytotoxic to cancer cells while sparing otherwise healthy cells in the process. Furthermore, additional evidence concerning the use of intravenous vitamin C for terminal cancer patients may improve symptoms and extend life (Padayatty et al. 2006). Importantly, a recent resurgence in the area of vitamin C therapy holds a biologically plausible explanation for why this approach could prove effective (SATOSHI Ohno et al. 2009) (Assouline and Miller 2006).

3.14.3 Vitamin D

It is well understood in the literature the impact low vitamin D levels have on overall health and specifically how low(er) levels lead to an increased susceptibility to infections. Furthermore, various epidemiological studies and observations have hypothesized a significant association among vitamin D sufficiency and the reduction of risk associated with various forms of cancer. Vitamin D levels are associated with both the incidence and new cases of cancer along with the morbidity of cancer as a whole (Kulie et al. 2009).

The vitamin D Council reports the association among 15 cancers and vitamin D deficiency (Hodgkin's lymphoma, non-Hodgkin's lymphoma, colon, esophageal, gallbladder, gastric, pancreatic, rectal, small intestinal, bladder, kidney, prostate, breast, endometrial and ovarian cancers). Dr. Jacob Cannell is a champion physician in the area of vitamin D and heads the vitamin D Council. Recent recommendations during a symposium held in 2008 included a warning message that the recommended vitamin D levels are too low, along with an important key point about having serum vitamin D levels tested, which is an extremely inexpensive blood test that renders valuable information about overall health and potential risk if levels are found deficient. This may prove particularly important among adolescents and young adults and is

paramount when considering the primary prevention of cancer (Cedric F Garland et al. 2009).

In a large portion of the world, individuals experience a seasonal variation in vitamin D levels that are the highest between July and September compared to very low levels in winter months. Interestingly, a Norwegian study published in 2005 in the British Journal of Cancer sought to examine the relationship between the seasonal variation in vitamin D levels and prognostic factors among HL patients. As such, they looked at what season in the year a patient was diagnosed and began treatment for HL and their corresponding vitamin D levels during the same time period. As previously established for breast, colon and prostate cancer, this study also found a significant improvement in the prognosis of HL related to seasonal variations.

Among patients who were younger than 30 years of age and diagnosed in the fall, the survival rates were 60% higher (Porojnicu et al. 2005). Although other explanations for the findings were considered such as better overall health status right after the summer months and because of vacations along with possible confounding issues due to an increased intake of fresh foods during the same time period which would increase antioxidants, researchers concluded such explanations did not impact the study results. In opposition to the positive findings surrounding vitamin D, the Cohort Consortium Vitamin D Polling Project of Rarer Cancers measured blood levels of 25-hydroxy vitamin D, which is the primary form of vitamin D and did not find any evidence to suggest higher circulating vitamin D levels were protective for endometrial, esophageal, stomach, ovarian, pancreatic, kidney and non-Hodgkin's lymphoma. In fact, among study participants, higher circulating vitamin D appeared to have an increased risk associated with pancreatic cancer.

Beyond the potential benefits in treatment among individuals with cancer, vitamin D therapy holds promise for prevention. There are particular methodological issues associated with this body of research that include small sample sizes of patients and a small representation of studies focused on rare cancers. Overall, more work is necessary to specifically understand the relationship between vitamin D levels and the prevention or recurrence of cancer. (A substantial list of research in the area of vitamin D and cancer is available at http://www.vitamindcouncil.org/researchCancer.shtml)

3.14.4 Chinese Medicine

There are no substantiated studies concluding that the use of Traditional Chinese Medicine is effective in treating cancer, although there is a biologically plausible argument for continued investigation and possible benefits from this traditional medicine that is used in China and been around for thousands of years. Interestingly, over one half of all the cancer agents in the United States currently being used for cancer treatment were originally derived from naturally occurring products (Chow and Huang 2010). As of late, there is a keen interest in plant based drugs such as recent work investigating silverstrol, which is showing promising results in specifically treating B-cell malignancies (Lucas et al. 2010). However, very few particular species of plants (which is estimated at over 250,000) are even considered for investigation (Chow and Huang 2010). Clearly, the possibility that Chinese medicine and specific herbs used to restore and maintain the balance of health in the body appears realistic (Chow and Huang 2010). Furthermore, identification of beneficial herbs used in Traditional Chinese Medicine along with rigorous research may lead to new discoveries in treating cancer using this historic approach.

3.15 Conclusions

The treatment for cancer in general remains obscure. When looking across all cancers and related research and clinical activity there is evidence of some improvement; however, when one examines the absolute numbers, considers the time and resources put in place over the past several decades to fight the war on cancer little progress has been made. Fortunately, one of the most successful treatable cancers is Hodgkin's Lymphoma. What one must remember is that regardless of the chemotherapy regime incorporated, it is only a matter of time until that same treatment will become ineffective and fail either because the patient cannot tolerate the toxic effects or will develop an overall resistance to the drug therapy (Chow and Huang 2010). Therefore, it is imperative that new therapies, which move away from current gold-standard approaches be developed and included as treatment options of people facing cancer. Furthermore, because of the impact late effects have specifically on HL patients, advancing treatment options through various modalities discussed is paramount in this cancer.

4.0 DISCUSSION: HODGKIN'S LYMPHOMA RESEARCH AND ACTIVITIES: WHAT ARE THE PRIORITIES?

4.1 Introduction

The preceding section of the report presented a holistic view of Hodgkin's lymphoma aimed at giving the Rasch Foundation and subsequent users an overall understanding of the disease from various perspectives. This section of the report will provide a discussion intended to take the knowledge gained and specifically highlight selected items for the Foundation to consider in either dedicating resources or pursuing collaborative partnerships with respect to HL in the future. It is imperative that all future funding in the area of Hodgkin's Lymphoma be directed to areas of need and to individuals and/or organizations, who will deliver tangible outcomes aimed at reducing the morbidity and burden of illness associated with Hodgkin's Lymphoma.

4.2 Targeted Therapies

Research activity into the development of new drugs for use in treating HL is a priority and reiterated in a recent publication from the German Study Group (Böll, Borchmann, and Diehl 2010). In considering all HL patients, who have undergone treatment for HL and the specific group that experiences a relapse subsequent to first-line interventions, new drug therapies are required to continue to reduce the burden of illness suffered as a result of the toxicity from conventional chemotherapy and radiation treatments along with offering patients experiencing a relapse additional treatment options. The development of specific biomarkers for targeted therapy could largely impact the 15-20% of individuals with early stages and approximately 30% with advanced stage who relapse after primary treatment (Persky 2007).

The median age of diagnosis for HL is 35 years. Given, the increased risk associated with standard conventional treatments, it is paramount to continue to investigate and understand pathways of treatment that use less toxic pharmacological agents along with developing therapies such as molecular targeting in order to progress to more personalized treatments for individual

patients. The biochemical details of emerging therapies including; monoclonal antibodies, CD30, CD20, CD40, CD80 and VEGF; bispecific constructs; immunotherapy and pharmacologic inhibitors are far beyond the scope of this report; however informative information is available through the publications of the German Research Group and a detailed summary found with the following citation (Böll, Borchmann, and Diehl 2010).

In general, the benefit of monoclonal antibodies is that they can provide a way to destroy the cancer cell without systemically attacking otherwise healthy cells as demonstrated in gold-standard treatments. This is important for HL patients, one there are substantial late effects from the gold-standard treatments, targeted therapies such as immunotoxins are designed not to affect the body systemically; therefore, patients and particularly younger HL patients can have their overall quality of life improved by reducing the secondary effects of treatment (Küppers, Yahalom, and Josting 2006). Second, there are a sub-group of individuals who do not respond to the gold-standard, primary level treatments and as such, targeted therapies can provide an additional treatment option if first line options fail. Finally, there is disagreement among clinicians whether or not patients presenting in the early stages of cHL require radiation therapy, again reducing the patient's exposure to toxic therapies by offering alternative therapies such as targeted treatments can largely reduce the late effects.

Researchers and clinicians working with monoclonal antibodies are focused on developing very specific antibodies, targeted to each of the HL tumor sub-types in the hope of replacing more systemic treatments with targeted therapies as a primary approach to treating HL. Once such monoclonal antibody, Rituximab has been used and despite the success of Rituximab for many patients with B-lymphocyte cancers, a percentage of patients either become resistant to this treatment thus, there is a need for research to expand the effectiveness of monoclonal antibodies. In HL, the composition of the tumor including finding abnormalities such as the RS cells is in fact quite rare (approximately 1-2% of the total tumor mass) thus, the study of the impact of molecular entities specifically designed to treat HL has not developed (Van Vlierberghe et al. 2009).

As noted, the International Prognostic Score is used to assess the level of risk a patient has at the time of diagnosis in how they will fair in treatment for HL. However, the current model of assessing risk cannot predict which patients will fail in treatment nor does it render any information on how a patient would do in treatment under-going a stem-cell transplant. Therefore, biomarkers are essential to have as new and additional pieces information to predict not only risk but overall survival. Further research is required in the area of biomarkers relevant to each sub-type of HL; however, "clinically relevant biomarkers have not been established to improve on the International Prognostic Score" (Steidl et. all, 2010. Abstract).

As mentioned, isolating particular RS cells in a HL cancer tumor is difficult as they are found in such few numbers. The number of RS cells found in HL tumors is very low; therefore, advancements in isolating and understanding the molecular structure and characteristics of the RS cell is progressing but at a slow rate. "The search for clinical and biological prognostic or risk scores that help in identifying patients at high risk for primary refractory disease or relapse has been only partially successful so far" (Böll, Borchmann, and Diehl 2010). Furthermore, there is considerable disparity across patients and sub-types of HL surrounding the number of RS in a tumor (Steidl et al. 2010). Although studies have examined the biomarkers of the RS cells more investigation is necessary, thereby improving the ability to not only assess risk but to do so for special patient populations (Sánchez-Espiridión et al. 2009) (Staege et al. 2008). Being able to identify those with a higher risk of poor prognostic outcomes would improve overall survival and treatment outcomes in HL and possible impact rates of toxicity and late effects of conventional therapy (Steidl et al. 2010).

Suggestions include more collaborative work on an international level in order to combine knowledge and use resources and available data more efficiently in order to create new therapies. This will require larger scale studies, international partnerships and dedicated funding to create the scientific environment where advancements in the understanding of biomarkers and resulting treatments specific to particular patient pathologies can happen. Developments in this area will impact the overall production of 'personalized therapies', which will help all cancer patients and specifically HL patients while simultaneously offer new and different treatments for patients who experience a relapse of their disease or build up an immunity to currently available

chemotherapy drugs (Savoldo et al. 2007). Of course, the hope is to advance in this area whereby personalized therapy is available to all cancer patients but of particular importance are those patients who have already tried drugs that are available and such pharmacological agents do not work or only work for a period of time.

4.3 Infectious Agents and Vaccines

From a research perspective, the goal is to find and identify the oncogene (a particular gene that in a specific quantity will cause a normal cell to change into a cancer and impedes cell death) associated with the EBV virus. Once again, this is difficult given how few HRS cells are found within a cHL tumor (Küppers, Yahalom, and Josting 2006). Continuing to develop primary prevention strategies surrounding infections associated with cancer such as vaccinations will pay-off two-fold, one the incidence of infectious disease will decrease and two, the associated risk and development of cancer as a result of such infections will also decrease over time. This may be particularly important in the developing world where advanced treatments are not always available thus; preventing disease in the first place becomes even more important.

As vaccinations have proved paramount in gaining control over a variety of infectious diseases, there is also the potential that developing vaccines on a large scale to target the infectious agents associated with the development of cancer and secondly to also use vaccines as a treatment option will also prove beneficial. The idea is to stimulate the body's own immune system through vaccination to deal with both the infectious agents associated with various cancers or to promote the body to deal directly with the cancer cells itself.

The vaccines provoke the body's immune system to create a specific antibody that will attach itself to the particular antigen that has invaded the body. In the case of infectious diseases known to cause cancer, the vaccine promotes the production of the antibody needed to kill the infection; thereby reducing the risk of getting the associated cancer. Well known is the Gardasil vaccine for HPV that causes the majority of cases of cervical cancer. Concerning infectious agents that cause cancer such as EBV and resulting HL cases, using a vaccination against EBV has the potential to dramatically reduce the number of HL cases that occur and significantly

impact the burden of disease. Similarly, the impact of the continued HIV epidemic, particularly in developing countries is also another infection that could substantially be reduced by vaccination and lead to a decrease in resulting cases of HIV associated cancers (Raabe and Kim 2010).

Beyond simply reducing infections, vaccines are an additional emerging treatment option in general. Creating vaccines using the specific antigens associated with cancer cells, results in the body producing the exact antibody needed to detect and kill the cancer cell. Research in the area of NHL, has developed a vaccine by doctors at the National Cancer Institute and was administered to 20 patients who were in complete remission. The vaccine was created from the patient's own lymphoma cells, which helped their immune systems, identify the residual lymphoma cells and eliminate them. Specific vaccination against infectious agents known to have a role in the development of cancer or using vaccinations to further develop a personalized medicine option for patients are two applications of vaccinations that may prove extremely beneficial in both primary and secondary prevention strategies surrounding cancer.

4.5 Nutritional Science

There is little doubt overall that it is possible to impact both the development and treatment of cancer through diet and nutrition. Despite the World Health Organization stating approximately 30% of cancers in the developing world and near 20% among developing nations is accounted for by some form of dietary factors, we are a long way from instituting the benefits of nutritional science into mainstream allopathic medicine or research.

Just recently, the Advisory Committee on the Dietary Guidelines for Americans, 2010 at the United States Department of Agriculture has recently released an update, which is done every 5 years and recommended a more plant-based diet for all Americans. The major issue to address in this revision is the number of Americans, who are currently overweight or obese along with under-nourishment, stating that too many Americans across all age gradients and both sexes need more vegetables, fruit, fiber and low-fat dairy products, citing a move toward a more plant-based diet will reduce obesity while also decreasing the incidence of chronic disease. In particular cardiovascular disease, some cancers and osteoporosis are listed as particular areas that could

realize improved outcomes with a plant-based diet (USAD 2010). Therefore, change is beginning in the right direction but there remains a great deal of work to do.

One of the major issues facing the advancement of nutritional science into mainstream research surrounds the issue of funding and resource allocation. The National Institute of Health (NIH) is comprised of over 20 specific institutes and surprisingly there is no single institute dedicated to nutritional science. In terms of financial resources, less than 5% of all funding in both the heart and cancer areas of the NIH focuses on diet and nutrition. When resources are dedicated in this area, the vast majority examine specific nutrients in isolation, which likely leads to serious methodological problems when attempting to discern the true nature of the relationship between overall health and diet (Campbell 2010). In the end, resources and specifically financial dollars dedicated to examining nutritional science is desperately needed. In conjunction with funding, the area requires investigators to move away from hypotheses focused on isolated aspects of nutrition, in other words individual nutrients and begin to advance the knowledge of the true relationships concerning nutrition by viewing nutrition from a more comprehensive approach, which builds on the work of Dr. Campbell and other researchers who have begun to unravel the impact diet can have on not only cancer but chronic disease as a whole. Furthermore, instituting nutritional science into Western medical training is long overdue. We must put forth the information about diet to new and upcoming physicians so they are better able to disseminate the benefits of diet to patients. It is not enough to lump diet into the modifiable risk factor group, for example simply suggest to patients they reduce their overall fat intake, we must better understand exactly what components of diet are required and to what degree it is necessary to omit certain substances in order to offset the damage being done by typical Western diets.

4.6 A Note on Special Populations:

4.6.1 Older Adults

A particular group among all individuals with HL are older adults (age 60 and over), who are diagnosed with HL. Individuals above age 60 have the poorest prognostic outcomes among all HL patients. It is thought that the overall estimation of the rates of HL among older adults is

underestimated and that many individuals will die prior to diagnosis. Interestingly, Boll and colleagues suggest that the bimodal distribution of HL (after age 55) is no longer observed, one reason being a majority of these individuals are actually diagnosed with a type of non-Hodgkin's lymphoma. This group fairs the poorest among all HL patients in terms of the complications, ability to tolerate and the toxicity of conventional treatments among other detrimental outcomes (Klimm, Diehl, and Andreas Engert 2007).

More research into particular interventions for this group is required as the majority of oldest HL patients are not included in clinical trials, thus outcomes found from current clinical trial research do not necessarily apply to this group. As the demographic trend continues toward a larger population base of older adults, it is suggested that research focus on continued new drug therapies for this particular group to address the growing demand of patients expected in the future.

4.6.2 Patients with Complications or Late Effects

As the incidence of HL continues to increase and our population ages, there is no reason to believe at this juxtaposition that the rates of lymphoma and specifically HL will decrease. Therefore, more people will be diagnosed with this form of cancer and undergo treatment to curb their disease. Additionally, the occurrence of HL among younger adults suggests that the issue of late effects or complications due to conventional treatment will continue. Priorities already noted such as primary prevention through diet and vaccines along with the development of personalized medicine will dramatically reduce the burden of illness associated with late effects. It is wholly important to address the risk of cardiovascular disease and the development of secondary cancers associated with treatments if we are to make the next major gain in the area of HL. Given such a large majority of individuals are successfully treated with current therapies, reducing the morbidity and mortality for those having already suffered from HL is an important consideration.

5.0 CONCLUSIONS

In concluding the environmental scan for Hodgkin's lymphoma, the key messaging is that a priority and emphasis must be placed on continuing to develop new conventional and alternative therapy options for individuals facing treatment for HL. In addition, research into primary prevention strategies including diet and the development of vaccines to control infectious diseases associated with HL could dramatically impact the number of new cases. The final recommendation to the Rasch foundation is to diversify the financial resources across research that will lead to a better understanding of the impact diet has both from a prevention and treatment perspective in Hodgkin's Lymphoma, while simultaneously supportive research and clinical activity focused on developing new and emerging therapies in order to reduce the late effects of conventional treatment.

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