

## Childhood cancers and systems medicine

William L. Stone<sup>1</sup>, Kathryn J. Klopfenstein<sup>1</sup>, M. J. Hajianpour<sup>1</sup>, Marcela I. Popescu<sup>1</sup>, Cathleen M. Cook<sup>1</sup>, Koymangalath Krishnan<sup>2</sup>

<sup>1</sup>Department of Pediatrics, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee, 37614, USA, <sup>2</sup>Department of Internal Medicine, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee, 37614, USA

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## 1. ABSTRACT

Despite major advances in treatment, pediatric cancers in the 5-16 age group remain the most common cause of disease death, and one out of eight children with cancer will not survive. Among children that do survive, some 60% suffer from late effects such as cancer recurrence and increased risk of obesity. This paper will provide a broad overview of pediatric oncology in the context of systems medicine. Systems medicine utilizes an integrative approach that relies on patient information gained from omics technology. A major goal of a systems medicine is to provide personalized medicine that optimizes positive outcomes while minimizing deleterious short and long-term side-effects. There is an ever increasing development of

effective cancer drugs, but a major challenge lies in picking the most effective drug for a particular patient. As detailed below, high-throughput omics technology holds the promise of solving this problem. Omics includes genomics, epigenomics, and proteomics. System medicine integrates omics information and provides detailed insights into disease mechanisms which can then inform the optimal treatment strategy.

## 2. INTRODUCTION

Pediatric cancers are the second most common cause of childhood death in developed countries (1). This review article focuses on childhood

# Nomenclature

- Omics: The large-scale characterization of an organisms/tissue macromolecules and metabolites, e.g., genomics, epigenomics, proteomics and metabolomics (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2392988/> )
- Genomics: Large-scale DNA sequencing and analysis (<https://www.genome.gov/18016863> )
- Epigenomics: Genome wide changes in gene expression not caused by changes in DNA sequence, i.e., changes in phenotype without changes in genotype (<http://www.whatisepigenetics.com/fundamentals/> )
- Proteomics: The large-scale characterization of proteins, their post-translational modifications and their interactions with other macromolecules (<http://proteomics.cancer.gov/whatisproteomics> )
- Kinomics: The global characterization of protein phosphorylation, kinases and phosphatases (<http://www.kinomecore.com/what-is-kinomics/> )
- Metabolomics: The large scale characterization of an organism metabolites, i.e., small organic molecules (<http://metabolomicssociety.org/metabolomics> )
- Signal transduction: The mechanisms (e.g. protein phosphorylation cascades) by which cells transmit molecular signals that regulate cellular functions, e.g. cellular growth or cellular apoptosis (<https://www.ncbi.nlm.nih.gov/books/NBK21205/> )
- Single nucleotide polymorphisms (SNPs): SNPs are single nucleotide substitutions that occur naturally in at least 1% of the general population (<http://learn.genetics.utah.edu/content/pharma/snips/> )
- Theranostics: A combination of therapeutics and diagnostics with the goal of optimizing individual patient treatment ( <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157283/> )
- Ominostics: A combination of omics and diagnostics with the goal of optimizing individual patient treatment.

Figure 1. Nomenclature with useful links.

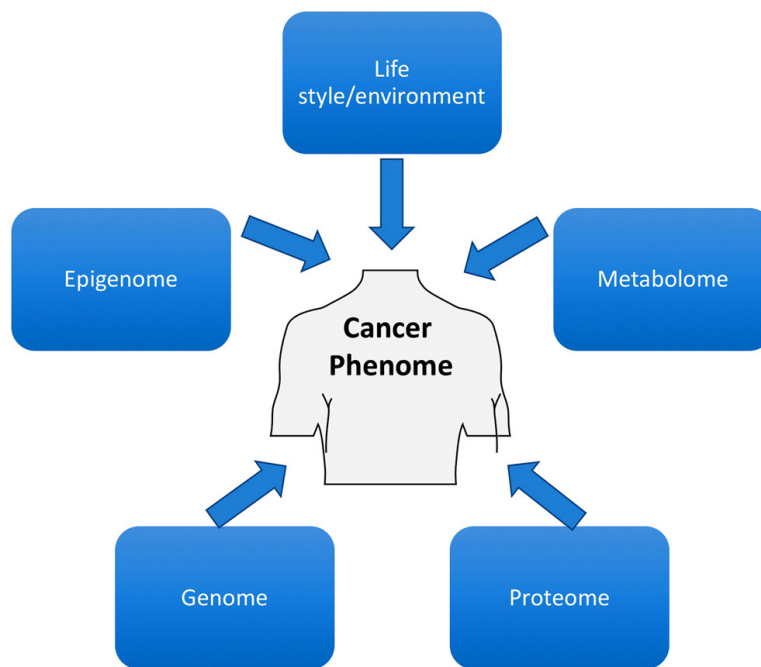


Figure 2. System Medicine. Simplified view of system medicine showing the contributions of the genome, the epigenome, the proteome, the metabolome and life style/environment to the cancer phenome (all of an organism's cancer phenotypes). In this simplified view, the multiple feedbacks and interactions between the various omics and between the omics and life style/environment are not detailed.

cancer from a systems medicine perspective and is intended for healthcare professional as well as researchers who want a broad overview of this rapidly advancing area. Liberal use of links to web pages is provided as a means of guiding the reader to useful resources and particularly lucid background information. Figure 1 provides a brief overview of the relevant nomenclature. The reader may also find the web page for the Sequence Ontology (SO) Project

very useful since it provides not only clear definitions of genetic terms but also a visual depiction of how these terms interrelate to one another (2). Systems medicine integrates the vast amount of data obtainable from omics technology into information that has clinical utility. This integration, while utilizing bioinformatics, does not ignore conventional medical knowledge or pathophysiology. As simplistically indicated in Figure 2, the genome, the epigenome, the proteome

(collectively called “omes”), obesity, lifestyle and the environment all influence the phenome. The phenome is the total of all observable phenotypes (attributes) in an organism. The definition of phenotype is not as straightforward as one might think (3). The modifier “observable phenotype” expands the classic definition of phenotype to include all the observable molecules in an organism, e.g., all the proteins (the proteome), all the metabolites (the metabolome), all the epigenetic alterations of DNA and RNA (the epigenome). This review will focus on the set of phenotypes relevant to pediatric cancers.

### 3. HOW ARE CHILDHOOD CANCERS DIFFERENT FROM ADULT CANCERS?

Cancer is a very heterogeneous disease with complex and tissue-specific causes arising from genetic/epigenetic and environmental factors (4). It is important to understand how childhood cancers are different from adult cancers since such an understanding could inform our knowledge of the underlying pathophysiological and molecular mechanisms and suggest new diagnostic/therapeutic approaches. Similarly, it is also important to understand how aging affects cancer. Although not a focus of this review, it has become increasingly clear that the relationship between aging and cancer is complex and not fully understood, e.g., life-extending genetic manipulations in animal models have been shown to attenuate cancer incidence and development (5). Below, we will briefly examine the causes of cancer, compare cancers in adults with those in children/adolescents and summarize what we know about the omics of childhood cancers.

#### 3.1. The three phases of cancer development

Cancer is a genetic disease caused by mutations in DNA and altered gene expression that ultimately results in uncontrolled cell growth. A complex web of signal transduction pathways is responsible for maintaining the normal growth and death of cells. Mutations that affect signal transduction pathways are responsible for most cancers (6). DNA is constantly damaged by reactive oxygen species (ROS), reactive nitrogen species (RNOS) and other endogenous compounds that are largely by-products of ongoing oxidative stress and chronic inflammation (7). Radiation exposure and exogenous carcinogens (e.g. those in cigarette smoke) also cause DNA damage. Most DNA damage is repaired before cell division occurs and does not result in a mutation passed on to daughter cells. Quickly dividing cells have less opportunity for DNA repair. If cell division occurs before DNA repair (a problem with rapidly dividing cells), the result can be a mutation. Most mutations are either harmless, or evoke apoptotic death in the mutated cell, and do not result in cancer.

Eventually, a cell can develop a mutation in a “driver-gene”, which promotes abnormal cell division (see below for more detail). This is called the “breakthrough phase” or phase 1 (8). Over time, cells with one driver gene mutation can accumulate a second driver gene mutation, giving rise to an “expansion phase” (Phase 2) characterized by the development of a benign tumor (8). For tumor cells to expand (or spread) they must develop vasculature (angiogenesis) or they would otherwise die (or be limited in growth potential) from hypoxia (9). There are at least a dozen or so proteins that either promote or inhibit angiogenesis (9). The third phase of cancer is the “invasive phase” in which at least one additional driver-gene mutation occurs in a surprisingly small number of molecular pathways (8). In the invasive phase, the cells in a tumor can detach from each other and pass through basement membranes to other tissues/organs, i.e. metastasis. In total, there are only about 200 driver genes out of the 20,000 genes in the human genome (8). An adult tumor typically harbors from three to eight driver gene mutations (10).

#### 3.2. Infectious agents, cancer and oncoviral vaccines

Infectious agents can indirectly promote cancer by causing chronic inflammation with an accompanying increase in the production of mutagenic ROS and RNOS (11). It is estimated that about 15-20% of worldwide cancers (both adults and children) are associated with viruses (12). Some viruses can directly cause cancer (direct carcinogen) by expressing viral oncogenes contributing to cancer cell transformation (11). Some viruses in the human papillomavirus (HPV) group and the Epstein-Barr (EBV) group are examples of cancer-causing viruses, i.e., oncoviruses. High-risk HPV infections are the primary cause of cervical, anal and oropharyngeal cancers in adults (13). HPV oncogenic viruses are highly relevant to pediatric oncology since childhood HPV vaccination is remarkably effective at reducing the types of cancers caused by these viruses. Moreover, DNA evidence suggests that HPV from infected mothers can be transmitted *in utero* to the developing fetus (14). The overall role of infectious agents in childhood cancers has been reviewed by Alibek *et al.* (15) and does an excellent job of evaluating the strong association of EBV infections and childhood leukemias. The American Cancer Society lists EBV infection as a key risk factor for acute lymphocytic leukemia (ALL) (16).

About 19 out of 20 adults carry the EBV and for most there are no serious symptoms (17). Nevertheless, EBV was the first identified human oncovirus and is associated with lymphoma. In children, there is a strong link between EBV infection and Hodgkin lymphoma (15). A key component of the Cancer Research UK “Grand Challenge” is to “wipe out

cancers caused by the EBV” by the future development of an EBV vaccine (17). The development of effective vaccines against oncoviruses is primarily a matter of strategic allocation of research funds followed by good public health policy. Our knowledge of how infectious agents contribute to cancer is still advancing, and it is likely that there are yet unknown oncoviruses. The importance of such knowledge is also manifested in an unexpected manner, i.e., the potential utility of using oncolytic viruses to kill cancer cells. This topic and its relevance to pediatric oncology and will be discussed below.

### 3.2.1. Oncolytic virus treatment for childhood cancers

In general, oncolytic viruses selective replicate in and kill cancer cells both directly and by stimulating an immune response. Early studies in the 1950s found that many wild-type viruses had an intrinsic ability to replicate in cancer cells and showed some promising anticancer effects. As reviewed by Seymour and Fisher (18), there has been considerable progress in the “rational design” of oncolytic viruses that has now resulted in FDA approval (2015) for treating advanced melanoma. This clinical progress will undoubtedly be further accelerated by detailed omic characterization of tumors which will provide the ultimate basis for selecting the optimal oncolytic virus treatment for a given tumor.

For childhood cancers, oncolytic virus treatment of solid tumors is particularly attractive since it could by-pass the life-lasting side effects of many chemotherapeutic agents (19-21). As pointed out by James Watson (22), most chemotherapeutic agents (including radiation) act by causing oxidative stress-induced apoptosis in cancer cells. Most cancer cells have a higher than normal level of intrinsic oxidative stress and only a small additional increment in oxidative stress caused by a chemotherapeutic agent is required to induce apoptosis. In addition to direct tissue damage, oxidative stress is genotoxic and causes an increased mutation rate with an increased risk of new cancers or cancer recurrence. Central nervous system tumors are the most common type of solid tumor in children, and current treatments are thought to give rise to long-term side effects in some children. Strategies for using oncolytic engineered herpes simplex virus-1 to treat pediatric cancers have recently been reviewed (19, 20) and hold much promise.

In the spirit of systems medicine, it should be noted that the genome of the oncovirus, the genome of the host as well as epigenetic alteration in both these genomes are considered important variables contributing to an individual’s susceptibility to oncovirus induced cancer (12). It is known, for example, that aberrant DNA methylation is quite

common in most tumors and can cause the silencing of tumor-suppressor genes (12).

### 3.3. Most cancers exponentially increase with age

It is well documented that the incidence of most cancers exponentially increases with age (23). This is attributed to the age-dependent accumulation of somatic driver gene mutations that affect tumor promoter pathways and/or tumor suppressor pathways. As pointed out by DeGregoria (23) this picture maybe overly simplistic since the rate of mutation accumulation is highest during the period from development to maturity (i.e., ontogeny) yet cancer risk dramatically increases from maturity to old age. Moreover, the cancer incidence in the general population levels off with advanced age and, quite remarkably, even declines in the oldest age groups (5).

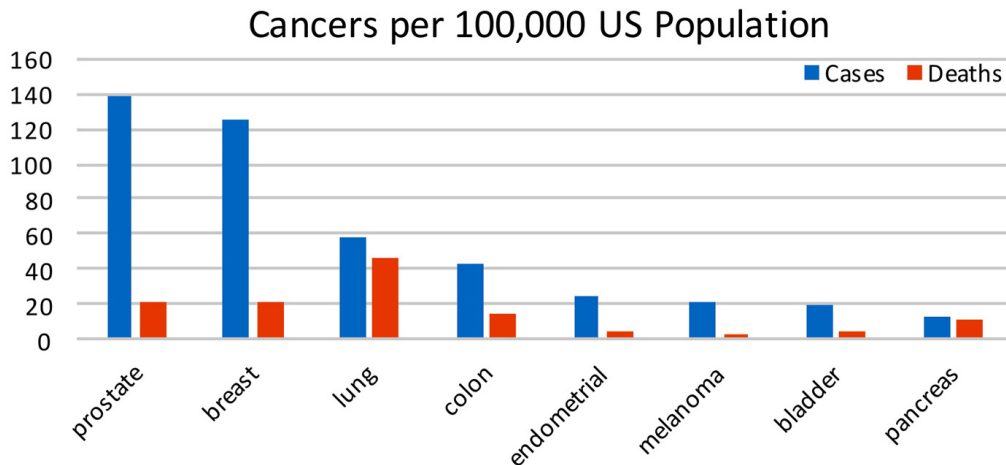
### 3.4. Adult cancers have a strong environmental component

As shown in Figure 3 (both by cases and deaths) the most common cancers in the general population are those of the prostate, breast, lung, colon, endometrium, skin, bladder, and pancreas. These cancers all have strong environmental/lifestyle components. Both prostate cancer (androgens) and breast cancer (estrogens) have a hormonal component that begins to manifest itself at maturity. Lung cancer, the primary cause of cancer deaths in both men and women, is primarily (about 90%) due to smoking cigarettes which is an enormous source of exogenous reactive free radicals, ROS, RNOS and other carcinogens (24). Considerable evidence suggests that diet and chronic inflammation due to the intestinal microbiome play key roles in colon cancer (25, 26). Skin cancer is strongly associated with exposure to the sun’s ultraviolet light (both UVA and UVB).

### 3.5. Obesity and childhood cancers

Obesity is increasingly recognized as a factor that markedly increases the risk of adult cancer, recurrence, and cancer mortality. A recent position statement from American Society for Clinical Oncology states that obesity is “quickly overtaking tobacco as the leading preventable cause of cancer”(27). A very large Israeli study has found, for example, that adolescent obesity is strongly associated with a future increased incidence of colon cancer in young to middle-aged adults (28).

The etiological links between obesity and cancer are not fully understood, and it is likely that multiple factors are involved (29). Obesity, like cigarette smoking, increases systemic inflammation and oxidative stress (30). The increased levels of insulin that characterize the early stages of obesity-



**Figure 3.** Incidence rates (cases) and death rates (per 100,000) for major cancers in the 0-19 age group by primary cancer sites for 2012. The incidence rates is from: [http://seer.cancer.gov/archive/csr/1975\\_2012/browse\\_csr.php?sectionSEL=28&pageSEL=sect\\_28\\_table.02.html](http://seer.cancer.gov/archive/csr/1975_2012/browse_csr.php?sectionSEL=28&pageSEL=sect_28_table.02.html) and the death rates from: [http://seer.cancer.gov/archive/csr/1975\\_2012/browse\\_csr.php?sectionSEL=28&pageSEL=sect\\_28\\_table.03.html](http://seer.cancer.gov/archive/csr/1975_2012/browse_csr.php?sectionSEL=28&pageSEL=sect_28_table.03.html). ONS : "other nervous system"; ALL: acute lymphoblastic leukemia.

related type 2 diabetes is thought to be a contributing factor to cancer since insulin is a growth factor (30). Insulin can also increase insulin-like growth factor (IGF), which is also a potent growth factor. The linkage of breast cancer with obesity in post-menopausal women is very strong and usually attributed to increased levels of estrogens released from adipose tissues (31). A recent study suggests, however, that obesity also causes structural alterations in breast tissue extracellular matrix structure in a manner that promotes tumorigenesis(32).

The potential links between obesity and childhood cancers is still under active investigation and has obvious world-wide significance. One fact that has emerged is an increased risk for obesity in adult survivors of childhood cancers (33). Cranial radiation exposure (to treat brain tumors) and glucocorticoid administration were strongly associated with an increased risk of obesity (33). Very much in keeping with a systems medicine approach, was the additional finding that SNP rs35669975, which is related to neural connectivity, might modify the risk of obesity among survivors exposed to cranial radiation (33). It should be noted that SNP rs35669975 is one of the SNPs (out more than hundreds of thousands) measured by the 23andme direct to consumer genetic testing service. SNPs are single nucleotide substitutions occurring in at least 1% of the general population. There is about one SNP for every 300 base-pairs; since there are about 3 billion base pairs in the human genome there are about 10 million SPNs.

### 3.6. Childhood cancers are different from adult cancers and have fewer mutations

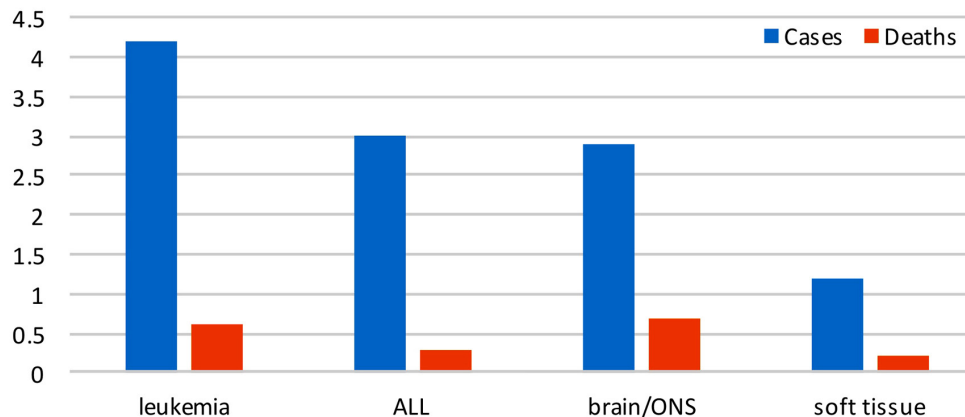
Figure 4 shows the primary cancers (cases and deaths) occurring in the 0-19 age group of the US

population. First, it should be noted that both cancer cases and cancer deaths are much lower than for the general population (Figure 3). Second, all the primary cancers in children/adolescents are different from those occurring in adults, and most have no obvious genotoxic environmental contribution (34). Leukemia and CNS tumors are the most common cancers in children. As shown in Figure 3, most adult cancers (e.g., lung, breast, prostate and colon cancers) are carcinomas (more than 90% of all cancers) which originate in epithelial tissue whereas most pediatric cancers (Figure 4) are sarcomas (about 1% of all cancers) which develop from mesodermal tissue. It should also be noted that the cancers seen in adolescents age 15 to 19 are very different from the 0 to 14 age group; the adolescents have more lymphomas due to an increase in Hodgkin's disease and also more melanomas/carcinomas (adult type tumors).

It is reasonable to suggest that adult cancers, having accumulated many non-specific environmentally induced genetic alterations, would have many more mutations than pediatric cancers. This suspicion is indeed supported by the data: lung cancers in smokers have ten times more somatic mutations than lung cancers from nonsmokers (10). Moreover, tumors and leukemias in children have about 9.6. mutations per tumor while the typical solid adult tumor has some 33 to 66 mutations per tumor (10). Although controversial, it should be noted that pediatric leukemias may have an environmental contribution since there is some evidence that radiation exposure from nuclear power plants (35, 36) and ground radon gas exposure (37) are a contributing factor. Nevertheless, the low number of mutations in pediatric leukemias suggests that environmentally induced mutations are not a major factor.



## Cancers per 100,000 US Population 0-19 Years



**Figure 4.** Incidence rates (cases) and death rates (per 100,000) for major cancers in the total population by primary sites. The rates are age-adjusted and based on 2009-2013 cases and deaths. These data are from <http://seer.cancer.gov/statfacts/>.

Prior exposure to chemotherapy is also an external risk factor for childhood cancer (38). As mentioned above, radiation and many chemotherapeutic agents act by inducing oxidative stress induced apoptosis in cancer cells. This therapy-induced oxidative stress is also genotoxic and can increase the rate of new mutations. An illustrative example is a recent work by Eleveld *et al.* (39); this group found an average of 15 nonsynonymous mutations in primary neuroblastoma tumors, but this number was markedly increased in relapsed neuroblastomas after chemotherapy/radiation treatment. As mentioned above, oncoviruses can also contribute to cases of childhood leukemia and lymphoma.

#### 4. GENOMICS AND INHERITED CAUSES OF CHILDHOOD CANCERS

##### 4.1. Genome wide association studies (GWAS) studies

In general, it has been suggested that pre-existing genetic/epigenetic alterations are major factors in causing childhood cancers (40). Defining the exact nature of these alterations is likely to provide useful individualized information for treatment including gene-based therapies (41). Although preliminary, it should be noted that a case of chemotherapy-resistant acute lymphoblastic leukemia (ALL) in a child was successfully treated using a DNA editing technique called TALENs (transcription activator-like effector nucleases) to modify donor T-cells so as to overcome graft-versus-host disease/rejection. These “universal” modified T-cells were then used in immunotherapy targeting a specific antigen on the malignant lymphocytes.

Genome-wide association studies (GWAS) are useful for looking for an association of a disease

with common SNPs and are a form of genotyping (<http://ghr.nlm.nih.gov/primer/genomicresearch/gwastudies>). The cost of obtaining a genome-wide SNP array is now about \$200, and such analyses are available on a “direct-to-consumer” basis, e.g., from 23andme.com. In contrast to GWAS, sequencing determines the exact sequence of base pairs in a DNA sample, e.g., the entire genome or just the exome which is the 1.5% of the genome that codes for proteins yet causes about 85% of genetic diseases. The cost of exome sequencing is dramatically dropping and is now about \$400 to \$ 1,500. GWAS studies usually require a very large sample size and were initially not thought useful for studying childhood cancers which occur at a much lower frequency than adult cancers (see Figures 3 and 4)(38). Nevertheless, GWAS studies have proven remarkably successful in showing an association of multiple SNPs with ALL, neuroblastoma, Wilm’s tumor, osteosarcoma and Ewing’s sarcoma (38). Most of the SNPs in these GWAS childhood cancer studies are reported by direct-to-consumer genetic testing.

##### 4.2. Genome and exon sequencing

Whole genome and whole exon sequencing can provide more detailed information than GWAS studies. The association of SNPs with a particular disease does not mean that these SNPs cause the disease since most SNPs are in introns, i.e., regions of DNA that do not code for protein. In contrast, whole exon sequencing only looks at DNA sequences in regions that code for proteins and is more likely to identify disease-causing mutations than GWAS.

Most genomic investigations of childhood cancers focused only on the alterations observed in cancerous tissues. As mentioned above, the consensus of these previous studies is fairly straightforward and

not unexpected, i.e., cancerous tissue from children presents a much less complex pattern of genomic changes since less time has passed to accumulate mutations arising from environmental and/or lifestyle factors (10). A very recent and comprehensive genomic study investigated the role of inherited mutations in childhood cancers (42). In the Zhang *et al.* (42) study the whole germline genome, the germline exome, or both were sequenced in 1120 pediatric cancer patients younger than 20 years of age with a median age of 6.9 years. The researchers focused on 60 genes that were associated with autosomal dominant cancer predisposition syndromes as well as 565 other cancer genes. The controls consisted of two cohorts of persons (966 and 515) whose whole exome had been sequenced and who had no known cancers. Pathogenic germline mutations were found in 8.5% of the pediatric cancer group whereas only 1.1% of the control group had such mutations (42).

### 4.2.1. Childhood cancers, TP53, BRCA1, BRCA2 and the future promise of CRISPR

The TP53 gene was the most frequently mutated of the genes associated with autosomal dominant cancer-predisposition syndrome and this gene codes for tumor protein p53, which is a potent tumor suppressor protein often called the “guardian of the genome” (43). TP53 mutations are known to be associated with “classic Li-Fraumeni syndrome” childhood cancers such brain tumors, acute leukemia, soft-tissue sarcomas, bone sarcomas, and adrenal cortical carcinoma. Despite being one of the most important and tumor suppressive protein it has been said that p53 “is as complex and enigmatic as it is relevant” (43). It has been suggested that lack of functional p53 decreases the effectiveness of standard chemotherapies and radiation treatment (44). Although not fully FDA approved, gene therapy strategies for repairing p53 dysfunction have been proposed and are currently in clinical testing (44)

There were some surprising additional conclusions from the Zhang *et al.* (42) study: (1) family history alone was not useful in predicting cancer predisposition syndromes; (2) mutations in *BRCA1* (BRCA1) and *BRCA2* (BRCA2) were detected in some of the pediatric cancers, yet these genes are not typically included in pediatric cancer genetic testing. *BRCA1* and *BRCA2* code for tumor suppressor proteins important in DNA repair. Moreover, *BRCA1* and *BRCA2* mutations were not found to be associated with any particular pediatric cancer. An immediate outcome of this study was the suggestion that next-generation genomic screening could be potentially useful in all pediatric cancer patients since such data could help guide clinical care. In particular, such screening would potentially allow oncologists to act early when

cancers are at their most curable stage. Moreover, genetic counseling could be beneficial to the parents and siblings of the affected children regardless of family history. In the not too distant future, it is also reasonable to suggest that genetic editing could be utilized to correct point mutations giving rise to critical cancer driver genes (45, 46). Although much progress has been made on revealing the genomic landscape of childhood cancers a recent NIH National Cancer Institute workshop concluded: “we need to further expand our knowledge of the genomics and epigenomics of childhood cancers” ([www.cancer.gov/news-events/cancer-currents-blog/2015/childhood-genomic-workshop](http://www.cancer.gov/news-events/cancer-currents-blog/2015/childhood-genomic-workshop)). The genomics/epigenomics of cancer recurrence after treatment was singled out as a key area for further study.

## 5. EPIGENETICS OF PEDIATRIC CANCERS

### 5.1. Epigenetics and cellular differentiation

Genomics has clearly made an enormous contribution to a systems medicine understanding of pediatric cancers. As mentioned above, pediatric cancers are characterized by a fewer number of mutations than in adult cancers and germline mutations in known cancer predisposition genes occur in only about 8.5% of pediatric cancers. It is possible, therefore, that other oncogenic mechanisms are in play, and a key culprit may lie in an inability of immature pediatric cancer cells to fully differentiate. Cellular differentiation is complex, involving many factors but epigenetic (i.e., non-DNA encoded) genome modifications are known to play a central role (47). It is not surprising, therefore, that epigenetic factors are increasingly being considered as critically important in pediatric cancers (48). Epigenetic mechanisms include (1) DNA and RNA methylation; (2) covalent modifications of chromatin; and (3) microRNAs which are small non-coding RNAs (19-24 nucleotides) playing a key role in regulating gene expression at the post-transcriptional level. Meseguer *et al.* (49) have written a particularly lucid review on microRNAs. Although not as well studied, RNA can also be modified by methylation and, in general, contains more modifications than DNA.

### 5.2. Differentiation therapy for childhood cancers

The advances in chemotherapeutic treatments for childhood cancers have been astounding and have now achieved an 80% five-year survival rate ([www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet#r3](http://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet#r3)). Nevertheless, conventional chemotherapeutic treatments can have late effects with serious long-term health consequences since many children/adolescents are now surviving into adulthood. Moreover, there are pediatric cancers that do not respond well to conventional chemotherapies and have a very poor prognosis, e.g., mixed lineage

leukemia (50). Consequently, there have been concerted efforts to develop targeted therapies that are: (1) less toxic than conventional chemotherapy; (2) effective in chemotherapy-resistant pediatric cancers; and (3) effective in preventing cancer recurrence. In these respects, differentiation therapy is an approach thought to hold much promise. The goal is to develop highly specific agents that promote the differentiation of cancer cells into mature cell types, which replicate at a slower rate and are susceptible to apoptotic death. 13-Cis-retinoic acid (RA) is a prototypic cellular differentiation agent, and it has been used to help prevent cancer recurrence after chemotherapy treatment for neuroblastoma, which is the most common type of childhood extracranial solid tumor. Neuroblastoma has its origin in neural crest precursor cells that do not undergo differentiation. RA treatment has proven to be effective at increasing survival rates yet about 50% of patients still, develop neuroblastoma recurrence (51). This poor outcome has provided the impetus to seek more effective agents for differentiation therapy. Strategies based on microRNAs are emerging as a key component of this impetus.

MicroRNAs are a class of epigenetic regulators that are abnormally expressed in cancers and play a key role in differentiation. These noncoding RNAs regulate gene expression by targeting the 3' untranslated region of target mRNAs thereby blocking translation (the primary event) and/or promoting the subsequent degradation of the target mRNA (49, 52). Broadly speaking, factors that block the microRNA biogenesis would block differentiation and be tumorigenic while factors that promote microRNA biogenesis could be anti-tumorigenic. Many microRNAs are downregulated in cancer, and it has been suggested, therefore, that re-expression of specific microRNAs could have therapeutic potential by promoting differentiation (c.f. (53)). A very good example of the potential of this strategy is illustrated by studies with rhabdomyosarcoma which is the most common pediatric soft tissue sarcoma thought to have its origin in skeletal muscle progenitor cells.

Zhao *et al.* (54) have addressed this issue and have developed an improved screening method to identify microRNAs with an ability to induce neuroblastoma cell differentiation. This group has not only found a set of novel microRNA that are potent inducers of neuroblastoma differentiation but have also characterized microRNA mimics that are more potent inducers of differentiation than current treatments. Nevertheless, the therapeutic use of microRNAs remains a difficult challenge and must await further research (55).

DNA methylation is a well-characterized (mostly stable) epigenetic alteration to DNA that modifies its function and plays a key role in normal

development, cellular differentiation and disease states (56). The role of DNA methylation in pediatric cancers has not been studied to the same extent as in adult cancers, but this situation is likely to change in the next decade. Both DNA hypomethylation and DNA hypermethylation methylation can promote cancer (57). DNA hypermethylation in a promoter region can silence gene expression: silencing tumor suppressor genes can thereby promote cancer. This simplistic picture is, however, complicated by findings showing that DNA hypermethylation in the "gene-body" region can have the opposite effect on transcription, i.e., activation of gene expression. The "gene-body" is best defined as the entire gene minus the promoter and untranslated regions. Jones (58) has written an excellent review of this topic which is beyond the scope of this paper.

## 6. PROTEOMICS OF CHILDHOOD CANCERS

Of all the omics technologies, proteomics is likely to have the greatest clinical impact on the rational design of targeted cancer treatments. Proteins are the nano-machines that ultimately perform, control and modulate cellular functions of key importance in cancer development, e.g., signal transduction pathways for cell growth, angiogenesis, differentiation, survival, apoptosis and immune functions. These complex functions are mostly modulated by post-translational modifications of proteins which cannot be fully predicted from genomic data alone. The phosphorylation of proteins by kinases and the dephosphorylation by phosphatases are key post-translational modifications important for cancer development and are often altered by driver mutations (59).

### 6.1. Kinomics and kinase inhibitors

Kinomics (Figure 1) is a specialized branch of proteomic technology that characterizes the global state of protein phosphorylation in an organism/tissue/tumor. Drugs that modulate protein phosphorylation, such as kinase inhibitors have a well-established role in cancer treatment (60). Kinase inhibitors, which suppress protein phosphorylation, have had an enormous positive impact on the treatment of some forms of pediatric cancers, e.g. chronic myeloid leukemia (60). Nevertheless, van der Sligte *et al* (60) point out that the use of kinase inhibitors for pediatric cancers is not nearly as well developed as for adult cancers despite the proliferation of new and promising kinase inhibitors. These authors convincingly posit that proteomics, kinomics, and advanced drug screening technology can "bridge the gap between pediatric cancers and the use of kinase inhibitors" (60). Knowing exactly how the kinome is disturbed in a childhood cancer can help define the kinases and phosphatases involved and thereby guide the rational use of kinase inhibitors.



In general, however, the use of proteomics in pediatric oncology has lagged behind that of genomics; this, in part, is because proteomics is not as amenable to high-throughput technology as genomics. Some private institutes and foundations are now focusing on proteomics as a key element in advancing the use of personalized medicine for the treatment of pediatric cancers (61, 62).

### 7. TUMORS ARE COMPLEX AND REQUIRE OMICS ANALYSES

The three phases of cancer development presented above (section 3.1.) is useful as a general framework but is overly simplistic since it superficially suggests that a tumor is just a mass of cancerous cells with growth issues. Cassady *et al.* (63) dispel this notion and suggest that solid tumors are “interconnected ecosystems comprised not just of cancer cells but also of numerous non-malignant cells.” As pointed out by these authors, the malignant cells, non-malignant cells, the tumor microenvironment and a complex mixture of cytokines, growth factors, and immunoregulators all play interconnected roles in promoting tumor growth and the ability to evade apoptosis (63). As indicated in Figure 1, systems medicine in a more integrative approach to understanding cancer phenotypes that encompasses environmental factors (e.g. viral infections and nutrition), obesity as well as the influence of an individual’s genome, epigenome, metabolome and proteome, i.e., omics data. There are only a few publications on the systems medicine of cancer (e.g., (64),(65) and fewer yet on the systems medicine of childhood cancers. Tian *et al.* (66) emphasize the utility of an omics approach in identifying diverse biomarkers that could be useful in pre-symptomatic diagnoses, evaluating disease progression, response to therapy and designing personalized therapy.

There are a number of major research centers which are now utilizing components of omics technology for the study and treatment of childhood cancers, e.g., Texas Children’s Cancer Center (67), Baylor College of Medicine (67), St. Jude—Washington University (the Pediatric Cancer Genome Project) (40) and the Children’s National Medical Center (68). The National Institutes of Health has embarked (2015) on a Precision Medicine Initiative with the expressed purpose of advancing biomedical research that will “provide clinicians with new tools to select the therapies that will work best for individual patients”(69). The National Cancer Institute will be an integral part of this effort, and a major goal will be to “assign patients to therapy based on the genetic alterations that are thought to be driving their cancer”(69). As detailed below, pediatric oncology will be a primary beneficiary of this approach since the genomic signatures for pediatric cancers are more straightforward than for adult cancers.

### 7. 1. Theranostics/ominostics for Childhood Cancers

Theranostics (see Figure 1) is usually defined as a merger between a diagnostic imaging methodology and targeted therapy. A major goal of theranostics is to pre-determine if an individual will be a likely responder to a particular therapy. It has been suggested that this approach will greatly improve the design and cost-effectiveness of clinical trials while decreasing the required trial size ([www.childrensinnovations.org/Pages/Highlights/Highlights-11.aspx](http://www.childrensinnovations.org/Pages/Highlights/Highlights-11.aspx)). The utility of theranostics is greatly enhanced by expanding the definition of “imaging” to include “diagnostic biomarkers”. The measurement of diagnostic biomarkers almost always involves an “imaging” step. For example, the use of a protein chip for the rapid and simultaneous detection of multiple tumor protein biomarkers utilizes chemiluminescence imaging (70). Researchers at the Boston Children’s Proteomic Center have used this expanded definition of theranostics to include diagnostic information from an individual’s genome/exome as well as proteomic data from a tissue/tumor or a body fluid ([www.childrensinnovations.org/Pages/Highlights/Highlights-11.aspx](http://www.childrensinnovations.org/Pages/Highlights/Highlights-11.aspx)). Theranostics is a perfect fit for a systems medicine approach to cancer since all the available omics data for a subject can be utilized to inform diagnostics and select an optimal targeted therapy. Nevertheless, a better term might be “ominostics” which we here define as “the use of omics data to design a targeted therapy.” The cost of omics data acquisition is rapidly decreasing and this, in turn, could affect healthcare costs in general. Targeted therapy, while potentially reducing the cost of drug development and dramatically improving outcomes, could increase direct costs to consumers; this is a much-debated topic (71).

The availability of direct-to-consumer genetic testing is now providing individuals with detailed genetic information having important health-related significance. While potentially promoting a proactive concern for health, direct-to-consumer genetic testing is not without many practical and ethical issues (72). Oncologists, and health care professionals, in general, must soon be prepared to provide guidance on these issues. The training of primary care physicians must rapidly be “updated” to keep pace with the rapid development of omics technology. Even genetic counselors may be overwhelmed by the enormous amount of health-related information provided by genomic analyses.

### 8. SUMMARY

A true systems medicine approach to pediatric cancers would entail integrating the data gained from genomics, epigenomics, proteomics and

metabolomics into an ongoing personalized treatment regimen that optimizes the choice of the treatment agent(s) while minimizing both short and long-term side-effects, i.e., omissions. As mentioned above, some academic institutions have already embarked upon efforts to use components of omics technology in pediatric cancer treatment. Nevertheless, it is probable that integrating data from multiple omics technology would be synergistic. Proteomics alone, particularly kinomics, may prove to be the most valuable of the omics technologies since it can directly inform about the altered phosphorylation signal cascades at the core of most cancer phenotypes. This information, in turn, can help guide individual drug treatment choices, e.g., kinase inhibitors. It is very encouraging that Cancer Moonshot 2020 recently announced the formation of a Pediatrics Consortium that will integrate genomics and proteomics analyses to help guide clinical trials (73).

## 9. ACKNOWLEDGEMENTS

This research was supported in part by the National Institutes of Health grant C06RR0306551 and the East Tennessee State University Robert W. Summers Pediatric Research Endowment. WLS wrote the first draft of this paper and all other authors equally contributed to the overall preparation of the final manuscript.

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**Abbreviations:** ALL: acute lymphoblastic leukemia; BRCA1: breast cancer 1 gene; BRCA2: breast cancer 2 gene; CNS: central nervous system; CRISPR: clustered regularly interspaced short palindromic repeats; EBV: Epstein-Barr virus; GWAS: genome-wide association study; HPV: human papillomavirus; RA: cis-retinoic acid; RNOS: reactive nitrogen oxide species; ROS: reactive oxygen species; SNP: single nucleotide polymorphism; TP53: tumor protein P53 gene; UVA: ultraviolet A (long-wave) radiation; UVB: ultraviolet B (short-wave) radiation

**Key Words:** Omics, Systems Medicine, Cancer, Oncology, Pediatric, Genomics, Epigenomics, Metabolome, Kinomics, Genome Wide Association Studies, Tumor, Theranostics, Ominostics, Review

**Send correspondence to:** William L. Stone, Department of Pediatrics, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee, 37614, USA, Tel: 423-439-8762, Fax: 423-439-8066, E-mail: stone@etsu.edu