



*EXPERIMENTAL  
DATA HAVE  
INDICATED THAT  
THE HOPE OF A  
CANCER CURE  
IS DEPENDENT  
ON THE  
IMPLEMENTATION  
OF TARGETED  
MOLECULAR  
THERAPY.*



*When a child is diagnosed with cancer, one of the most important jobs as physicians is to give hope to the young patient's family while also dispensing facts. While the diagnosis may seem devastating, the facts often give the family reason for hope.*

## **BIOREPOSITORY FOR CHILDHOOD TUMORS**

**HOW MOLECULAR DIAGNOSIS IMPACTS TREATMENT AND SURVIVORSHIP**

*This optimism is based on the fact that cancer treatment for children has improved dramatically during the past few decades. Fifty years ago, the five-year childhood cancer survival rate was dismal—less than 25 percent. Today, the survival rate is more than 75 percent.*

Although the survival rate has improved significantly, there is not yet a cure. The collaborative work of the Children's Oncology Group (COG), which involves a team of pediatric oncologists, pathologists and surgeons who keep pace with the dynamic changes of protocols of the morphologic classification of tumors, was one of the key reasons for the immense improvement in childhood cancer survival.

However, with the revolution of the molecular field, pathologists learned that the current diagnostic tools are limited and that molecular and genetic classification of cancer is superior to morphologic classification. The available data suggest that the molecular analysis of tumors with the subsequent understanding of the molecular genetic basis of cancer will be the best chance for finding a cure for childhood cancer. Thus, physicians are hopeful that significant improvements in treatments for pediatric cancer patients lie ahead in the not-so-distant future.

According to the National Cancer Institute, "the lack of standardized high-quality biospecimens represents the significant roadblock to cancer research." Keeping this in mind, Children's Healthcare of Atlanta started its tumor biorepository. This was an important step for healthcare in Georgia because approximately one new pediatric malignancy a day is diagnosed in the state, including leukemias and brain tumors. It is a crucial time to start the biorepository because Children's has a growing hematology and oncology practice at the Aflac Cancer Center and Blood Disorders Service of Children's. The Children's Neurosciences program, which focuses on research of childhood brain tumors, also is growing. Children's is aiming to become the central pediatric tumor biorepository for the state of Georgia in collaboration with the Georgia Cancer Coalition. The goal of the tumor biorepository is to collect high-quality RNA and DNA samples of tumors for further molecular analysis and, as a result, a strict protocol for collecting tumor specimens was implemented at Children's. Specimens are frozen within 10 minutes of collection in the operating room and a frozen section from the sample is taken to confirm tissue quality. Children's now has more than 1,400 frozen tissue samples in its tumor database.

The focus on molecular analysis of tumors from frozen tissue came from the learning that this tissue will provide the best genomic information about tumor cells. Traditional formalin fixation damages DNA and genomic materials. Frozen tissue, however, allows for a better molecular biological analysis of the tumors, which will allow for better understanding of cancer genomics, as well as initiate the design of specific therapy in the form of targeted pharmacogenetics. The importance of this discovery cannot be overstated: all experimental data indicate the hope of a cancer cure is dependent upon the implementation of targeted molecular therapy. Using these new regimens will minimize the short-term and long-term side effects

*Childhood tumors were recorded as early as 1500 B.C. in the Ebers Papyrus, one of the world's oldest preserved medical documents. At that time, recommended treatments were pharmacological, mechanical or magical. Rudolf Virchow, the father of modern pathology, began the systematic study around 1850 in Berlin. Following Virchow, James Ewing recognized the correlation between the growth of malignant tissue and the maintenance of adequate blood supply to the tumor. (Interestingly, the Ewing's sarcoma family of tumors serves to illustrate the power of molecular diagnostics. Bone and soft-tissue tumors were shown to share a common underlying molecular pathogenesis).*

*The vast majority of the discovery of new diagnostic tools occurred in the last century. In 1930, electron microscopy was discovered. In the 1940s, immunohistochemistry was utilized as an additional diagnostic tool. In the 1980s polymerase chain reaction was employed followed by tissue microarray in the 1990s. However, the most important turn in cancer diagnostics started in 2000 with the new focus on the Human Genome Project, which includes the study of proteomics and metabolomics. This breakthrough helped shed more light on the molecular and genetic basis of malignancies.*

of current cancer treatments.

One future goal for the biorepository is to save nontumor tissue (fibroblastic cultures) and blood samples from every cancer patient. Molecular and biochemical analysis of the patient's normal tissues will allow for a comparative genomic hybridization between normal and malignant cells. This will shed some light about the genomic makeup of the patient and will provide data about whether the patient has a genomic predisposition to cancer.

An example of this analysis is that the somatic (normal) cells might show a deletion or translocation that allows a cancer-promoting gene to be amplified, thus promoting cancer in the patient. The advantage of collecting both fibroblastic cultures and blood samples lies in the fact that many tumors arise from mutations in either somatic or germline genes. And, fibroblastic cultures are important, especially in cases when blood samples contain limited genomic material, as in immunosuppressed patients. Blood samples are easy to obtain and inexpensive to study. And, in patients with metastatic disease, messenger-RNAs (m-RNAs) can be detected in blood samples, which will allow us to detect the presence of second malignancy or recurrence early. Additionally, having this data about the genomic makeup of these cancer patients will allow physicians to understand the cause of a second malignancy if it occurs.

In the United States, one in every 570 adults is a survivor

of pediatric cancer. Of those patients, 73 percent have chronic health problems, 42 percent of which are severe, disabling or life-threatening. The most severe long-term effects—growth, learning disabilities, infertility and secondary malignancies—can be related to radiation exposure in childhood. Collecting all of the molecular information will help better explain whether second malignancies are a result of chemo or radiation therapy or because a patient was predisposed to this malignancy due to a specific mutation in his genomic makeup.

An important addition to this program is to provide genetic counseling to every cancer patient to obtain an accurate pedigree of patients' families. This will provide the treatment team with any history of cancer and will help siblings and other biological relatives of the cancer patient to become aware of the presence of any familial cancer predisposition.

Although analyzing molecular data is more costly than conventional histology because it requires frozen tissue expertise in handling tumor tissue and expensive equipment, it should not be viewed as a prohibiting factor. The truth is, we cannot afford not to use molecular diagnostics. This analysis and the subsequent data will provide us with precious information that will improve the treatment and long-term survival of these pediatric patients, and ultimately provide them with a better quality of life.

### The role of the primary care pediatrician

One major step toward the early detection of childhood cancer is through a comprehensive examination during primary care routine visits. When a malignancy is suspected, an immediate referral is warranted. The pediatrician's role will be to support and educate the family and explain to them the available tools and programs that will help them during this difficult time, including the importance of molecular analysis of the tumor and the existence of resources like the Aflac Cancer Center Cancer Survivor program. The program aims to improve our understanding of risk factors; to manage late effects of cancer and its treatment; to support survivorship research with new initiatives focused on cancer patient follow-up; to bank significant numbers of tissue samples linked to clinical and outcome data; and to end workplace and health insurance discrimination. ©

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#### For more information:

The **Aflac Cancer Center Cancer Survivor program** Web page offers educational information about long-term follow up after cancer diagnosis and treatment.  
[www.choa.org/cancersurvivorship](http://www.choa.org/cancersurvivorship)

The **National Cancer Institute (NCI)** offers a primer on biorepositories and their role in research, including a list of frequently asked questions and appropriate answers.  
<http://biospecimens.cancer.gov/basics/faqs>

The final version of the **NCI Best Practices for Biospecimen Resources** has been accepted by the National Cancer Advisory Board and is now available. This document outlines the operational, technical, ethical, legal and policy best practices for NCI-supported biospecimen resources.  
<http://biospecimens.cancer.gov/practices>

The **Children's Oncology Group (COG)** is dedicated to curing and preventing childhood and adolescent cancers. The COG also offers individual and institutional memberships, seminars and training.  
[www.childrensoncologygroup.org](http://www.childrensoncologygroup.org)

The **Georgia Cancer Coalition's** Web site offers an array of information, including data, clinical trials and survivorship issues.  
[www.georgiacancer.org/prevent.php](http://www.georgiacancer.org/prevent.php)

More information on the **Human Genome Project**, which was completed in 2003, is available from the U.S. Department of Energy's Office of Science.  
[www.ornl.gov/sci/techresources/Human\\_Genome/home.shtml](http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml)  
A brief overview from the National Institutes of Health also is available.  
[www.genome.gov/12011238](http://www.genome.gov/12011238)

