

# Deep Exome Sequencing Helps Researchers to Discover Causative Mutations

The HiSeq® 2000 system and TruSeq® Exome Enrichment Kits are enabling GTAC studies and helping researchers discover mutations in cancer and constitutional disorders.

## Introduction

Seth Crosby, M.D., is Director of the Genome Technology Access Center (GTAC), which provides next-generation sequencing (NGS) services to the global research community. As an expert in genomics, Dr. Crosby consults with principal investigators on experimental design and data analysis to ensure his clients' results support their specific aims.

Dr. Crosby uses exome sequencing to analyze the complex biology of mutations. The massive throughput, accuracy, and cost-effectiveness of the HiSeq 2000 system, combined with TruSeq Exome Enrichment, have enabled his customers to tackle these and other complex questions that were limited to well-funded investigators and consortiums only a few years ago.

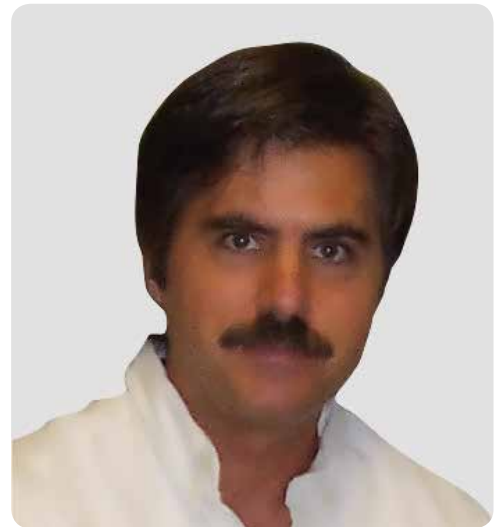
## At the GTAC, the Emphasis is on Access

At the GTAC, which is part of Washington University in St. Louis, the emphasis is on access, servicing researchers in industry, government, and academia worldwide. "We are an Illumina Certified Service Provider (CSPPro®)," says Dr. Crosby, "and we've consolidated all of the molecular services under a single umbrella. This structure, combined with the Illumina technology that we leverage, helps us to achieve economies of scale and increases the flexibility in what we can ultimately provide to our customers." The GTAC accommodates projects of all sizes, ranging from two to more than 2,000 samples.

## Making Scalable Exome Sequencing Affordable

"Most questions being asked here have to do with heredity," explains Dr. Crosby. "People are looking at exomes and trying to determine if any changes in the exomes correlate with heritable traits." Dr. Crosby estimates that 90% of human sequencing projects currently performed at GTAC are exome sequencing. "We do a lot of exome work," says Dr. Crosby. "With HiSeq we can load more samples per flow cell and sequence more for less. It's just that simple. It enables us to pass the cost savings on to our customers."

Dr. Crosby describes the workflow for the TruSeq Exome Enrichment Kits as straightforward and easy. "The pre-capture pooling is a major selling point for Illumina," he says. "We did a bake-off between Illumina and two other competitors and we found that the Illumina pre-capture pooling worked very nicely and generated data that was either comparable or better than the others." He adds, "ease of use and uniformity of coverage aside, Illumina offers about 25% more real estate. Our best experience has been with Illumina. The impact is that the cost is significantly lower." Dr. Crosby also



Seth Crosby, M.D., Director, Genome Technology Access Center, Washington University at St. Louis

"With the HiSeq, we can sequence deeply enough that we're not only able to discover mutations, but we can also find very rare mutations, like a needle in a haystack."

adds, "Illumina support is absolutely fantastic. This is critical as sequencing technology is still in development." He acknowledges, "you can talk about cost per megabase and error rates, but Illumina stands behind and invests heavily in their technology."

## HiSeq is Enabling Accurate, Deep Exome Sequencing

The GTAC has a partnership with the Division of Genomics and Pathology Services (GPS) at Washington University, working on studies to determine important mutations in cancer. "We are using exome sequencing on the HiSeq to analyze various genes and various cancers," Dr. Crosby describes. "We're looking not only at indels or polymorphisms, but we're also looking to see whether the chromosomes have recombined in a way that's oncogenic."

Finding causative mutations within tumor cells is challenging. Making matters more complicated, cancer cells are not clonal. Cancer cells lose the ability to proofread genetic material after repeated divisions. As the cancers grow, different mutations are incorporated into different cells. Normal tissue can be laced throughout solid tumors, and in some cases, genetically different tumor cells are found within solid tumors.

"We can overcome this challenge with accurate, deep sequencing on the HiSeq," says Dr. Crosby. "Samples from a number of patients can be combined into a single HiSeq lane. With the HiSeq, we can sequence deeply enough that we're not only able to discover mutations, but we can also find very rare mutations, like a needle in a haystack." He adds, "even if only 20% of the biopsy is tumorous tissue, or even if multiple clones exist within the tumor, the HiSeq allows us to sequence so deeply that we can still find those mutations."

According to Dr. Crosby, "our customers are very happy with the accuracy that Illumina technology provides." He adds, "if we were to try and discover mutations using Sanger sequencing, we would be lost because each position is simply indicated by a peak."

## HiSeq is Changing the Landscape

When asked about the impact HiSeq has had on sequencing, Dr. Crosby says, "HiSeq is democratizing sequencing." He explains, "it's allowing new investigators to ask questions that only a lucky few at elite institutions used to be able to ask just a few years ago. The technology is moving so fast that the research community is still trying to determine the potential of new applications and what can be done today." Dr. Crosby concludes, "it's a completely different world now compared to how things were just a couple of years ago."

Learn more about the HiSeq 2000 system and TruSeq Exome Enrichment Kits at [www.illumina.com](http://www.illumina.com)

## Summary

### Overview

The Genome Technology Access Center (GTAC) provides next-generation sequencing services to the global research community. The GTAC is an Illumina Certified Service Provider (CSPPro).

### Challenge

The GTAC helps guide researchers through experimental design and analysis using the latest sequencing technologies to achieve their goals. Many studies involve looking at exomes and trying to determine if changes in the exomes correlate to heritable traits.

### Solution

The GTAC is using the HiSeq 2000 system and TruSeq Exome Enrichment Kits to sequence human exomes. Through exome studies, researchers are trying to discover causative mutations in cancer and constitutional disorders.

### Benefits

Illumina technology helps the GTAC to provide their customers with access to powerful, accurate, cost-effective sequencing studies.

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