On July 11, 2012, New York Times readers were introduced, posthumously, to Rory Staunton, a 12-year-old Queens resident who embraced social-justice issues and was taking flying lessons.

Rory came home from school on a Tuesday with a cut on his arm, the result of diving for a basketball in gym class. He died that Sunday from septic shock, a severe form of sepsis. Sepsis is a potentially life-threatening complication triggered by the body’s response to infection.

The Times story helped raise awareness about sepsis, an illness that kills more than 200,000 people in the United States annually, according to the Centers for Disease Control and Prevention – more deaths than breast, colorectal, pancreatic and prostate cancer combined. Worldwide, estimates suggest that perhaps more than 5 million people die each year of sepsis.

The year before Rory’s death, a report from the federal Agency for Healthcare Research and Quality indicated that hospital stays for sepsis more than doubled between 2000 and 2008. Researchers have stepped up efforts to better understand this illness, and JMP Genomics is playing a vital role.

In 2013, JMP Genomics software from SAS helped a team of researchers develop a blood test that predicts the progression of sepsis through the body, forecasting whether it will take the form of a mild infection or a catastrophic illness. Now, they aim to devise a hand-held device that physicians can use to quickly determine appropriate treatment. Stephen Kingsmore, Director of the Center for Pediatric Genomic Medicine at Children’s Mercy Hospitals and Clinics in Kansas City, MO, leads the research team.

“JMP Genomics was our primary method of assessing data quality, performing data transformations, data visualization and data analysis,” says Kingsmore, the former President and CEO of the National Center for Genome Resources.

From standard quantitative genetic analysis with mixed models to complex association mapping, JMP Genomics...
has been deployed in studies that have explored schizophrenia, the potential use of prairie plants for biofuels and much more. The software combines the point-and-click access and dynamically interactive graphics of JMP with the powerful analytics of SAS for exploration of vast genomics data sets.

“There’s no way I could have done this work using typical statistical programs and methods. JMP Genomics was key to its success,” says Ray Langley, Associate Research Scientist at the Lovelace Respiratory Research Institute in Albuquerque and lead author of a journal article about the study. 

“This was a tour de force, given the amount of data we had to sift through,” Langley says. “I believe it was a ground-breaking clinical study in regard to the number of patients and clinical factors; the cutting-edge technologies we utilized; and the multiple data sets that were gathered, analyzed and validated. I believe this will provide an outline on how to study complex heterogeneous diseases in the future.

“And it all came down to letting the data tell the story.”

Mapping the illness
Sepsis is caused by the spread of infection throughout the body. It can lead to failure of the lungs, kidneys and liver. Triggered by the immune system’s response to infection, sepsis develops when chemicals released into the bloodstream to fight the infection overreact, causing inflammation. Symptoms include high fever, flushed skin and an elevated heart rate. In severe cases, blood pressure drops dangerously low and organs shut down. Death can occur within hours.

Langley joined this research project in 2008 while doing post-doctoral work at the National Center for Genome Resources. The primary objective was to help doctors determine whether a patient had sepsis, and then to help predict its progression. Patient testing had begun in 2005 at Henry Ford Hospital in Detroit and at Duke University Medical Center and the Veterans Affairs Medical Center, both in Durham, NC. More than 1,000 subjects were tested over four years. From those subjects, Langley selected a subset of patients and studied infection status, progression and outcomes using a systems biology approach.

“It’s very difficult to understand what path sepsis will take,” Langley says. “Will it take a simple course, or will it quickly progress to septic shock and, potentially, death?”

Predicting the likely path for individual patients would allow doctors to undertake appropriate treatment quickly.

Langley and his colleagues examined the metabolites (measures of the body’s ability to produce energy, and thereby fight infection) and proteins of patients with and without sepsis – first upon their arrival at hospital emergency departments and again 24 hours later. They found considerable differences

between patients who died and those who survived.

An algorithm to predict survival factored in such considerations as age and red blood cell count along with the measurements of five metabolites. This algorithm will be used to help inform treatment procedures.

‘I’m not a statistician’
The research involved a great deal of data. In studying changes in RNA molecules, for example, some 30,000 genes were examined.

Typically, such studies would require a server-based analytics program, Langley says, “and you have to have a pretty strong programming background to use those tools. I’m not a statistician or a programmer; my training is in immunology.

“So JMP Genomics was quite nice, in that it allowed me to use a simple GUI-based program to quickly analyze these large data sets without much difficulty,” he says.

Langley used principal components analysis in JMP Genomics to establish whether the data clustered as expected, and then ran analyses of variance, or ANOVAs, to determine statistical differences.

Predictive modeling was another feature of JMP Genomics that proved invaluable.

“I typically use logistic regression, but there are a number of different methods that can determine which metabolites are predictive of outcomes,” Langley says. “JMP Genomics allows for a lot of predictive reduction, so you have less risk of overmodeling, which can be a big concern using these tools.”

Langley used the software to validate his training sets. In addition to its own data, the team had data from the Boston-based Brigham and Women’s Hospital Registry of Critical Illness (RoCI). “I was able to quickly train on my data set and then validate using the RoCI data set,” Langley explains.

Once the data was compiled, the team sent it to a statistician who performed a

Global cross-correlation analysis of metabolomic and proteomic data of matched patients allows for potential discovery of both known and unknown enzymatic reaction models.
Kingsmore, the research team lead, is likewise a JMP Genomics enthusiast. “The ability to handle 10 million rows of data is impressive,” he says, “especially when doing analysis on a laptop.”

He finds the software’s variance decomposition tool easy to use and helpful in determining whether a data set can test a hypothesis, and then in defining fixed effects for analysis of variance to assess the hypothesis.

Kingsmore also likes the ability of JMP Genomics to perform Boolean functions, its data-transposition capabilities and the merge function.

Go-to software

Late in 2013, there was still much work ahead on the sepsis project, and the team was developing a prospective validation analysis. “The main thing is to see if our test holds up,” Langley says. “We want to make certain it is accurate before we consider putting it in the clinic and making patient management-protocol decisions.”

The long-term goal is to help develop a handheld point-of-care device that will let clinicians diagnose sepsis and predict the severity of the illness within hours – a tool that might have saved Rory Staunton’s life.

“If you can identify the patients that appear to be on a course to a catastrophic outcome, then you know you’ve got to throw everything at them,” Langley says. “You’ve got to treat them aggressively. And I believe that there are potential therapeutics out there that we might soon begin to test preclinically that may improve outcomes.”

He says that there’s a lot of momentum now behind this research. Another ambition is to apply the research findings to a range of other infectious diseases, including the flu.

While this research project was Langley’s first experience with JMP Genomics, he says it certainly won’t be his last. He’s now working with a nonhuman primate model of sepsis, comparing metabolites with lung RNA molecules. Langley is using JMP Genomics to examine how they associate, and to then build hypothetical association models.

“I use it pretty much all the time now,” Langley says. “For anything with a complex data set, I’ll be using it.”

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