**SUSAN L. COHN:** Hello, I'm Susan Cohn, Professor of Pediatrics at the University of Chicago Medicine, Comer Children's Hospital, and Dean for Clinical Research. I'm going to give you an update on advances in neuroblastoma classification and treatment, through collaborative research.

Neuroblastoma is a clinically heterogeneous disease. There are subsets of patients that will undergo spontaneous regression without any therapy whatsoever. Others that are cured with moderate dose chemotherapy and surgery. And then a third subset of patients who unfortunately have disease that's very resistant and refractory to treatment, and these children have a very poor outcome.

We currently tailor treatment according to the patient's predicted clinical behavior. In the children's oncology group we use a risk group schema that includes the patient's stage, age, and mix status, tumor cell ploidy, histology, as well as some other characteristics, to classify patients into either low, intermediate or high risk groups. And then subsequently patients receive therapy that is tailored according to their risk.

As you can see from the survival curve, our current treatments are quite successful in treating patients who have low and intermediate risk. But unfortunately, patients who are classified as high risk continue to have relatively poor outcome. And much more work needs to be done to develop better therapies for patients with high risk disease.

Now one of the problems that we have is that the criteria that are used by cooperative groups around the world are not uniform. So although that was the Children's Oncology Group class risk classification, in Europe and in Japan, different cooperative groups use different classification systems. And it's therefore not possible to directly compare the results of clinical trials that are performed in different regions of the world, because the children that are going on those studies are apples versus oranges.

So in 2005 I helped co-chair a task force with my colleague, Andy Pearson from the UK. And our goal was to develop a uniform classification for pre-treatment risk, stratification for neuroblastoma patients around the world. And we gathered an international cohort of investigators, and we set up a meeting in Whistler, Canada, to accomplish this task.

We successfully were able to collect data on 11,000 children with neuroblastoma from around the world, including the analytic cohort, that consisted of 8,800 patients that were diagnosed between 1990 and 2002. We analyzed the statistical and clinical significance of 36 prognostic factors, using survival tree regression analysis. And we subsequently analyzed the most powerful factors that were prognostic of event free survival, and subsequently established the INRG classification and staging systems. The survival tree regression analysis revealed that the seven most highly significant factors included stage, age, histologic category, grade of tumor differentiation, N-myc status, the chromosome 11q status, as well as DNA ploidy.

This is a picture of the table that we generated by analyzing the data. And as you can see, it is a little bit different from the Children's Oncology Group classification system. We're now using the INRG stage. Age is calculated in months, with 18 months being a cut off. Histologic category is included in this particular classification system. The grade of tumor differentiation, N-myc status, 11q status, ploidy, and then patients are subsequently stratified into risk groups that include very low, low, intermediate or high.

These classification systems and the staging systems have been published in *The Journal of Clinical Oncology.* And we have also published a number of different consensus reports, to determine how to perform molecular diagnostics, how to evaluate minimal residual disease, how to evaluate extensive disease using MIBG scans, as well as in imaging and staging classifications.

The INRG classification system will ensure that all children with neuroblastoma are stratified into homogeneous pre-treatment groups. They'll ensure that tumor biology and responses are evaluated in a similar manner across the world. And it will greatly facilitate the comparison of risk-based clinical trials conducted in different regions of the world, and provide a platform to ask additional randomized questions, and will also lead to the development of international collaborative studies.

I'm happy to report that the cooperative groups SIOPEN, which is the European cooperative group, as well the Children's Oncology Group, which is a North American cooperative group, have already begun to integrate the INRG risk schema into their upcoming clinical trials. And so now the INRG classification system will enhance our ability to compare apples to apples.

This cohort of patients is the largest cohort that has ever been collected. And we currently have over 18,000 patients in our INRG cohort. And we recognize that this was a very, very valuable resource, and so we have made these patient data available for data mining projects. And investigators from around the world are able to apply to conduct research studies using this database. We very successfully have already conducted a number of data mining studies, several of which have been seminal and published in very high impact journals. These data allowed for studies in very small cohorts of patients that otherwise would never been possible.

However, very much like the Children's Oncology Group classification system, there are some limitations to the INRG data. And that is largely the fact that these prognostic factors are very old, more than 30 years old, and they don't include any of the new molecular prognostic factors that have more recently been described. New technologies are now available for genome-wide analysis, and there have been a plethora of studies demonstrating the prognostic significance of a number of different omic signatures, array CGH, as well as sequencing of neuroblastoma tumors. And there have also been some very intriguing data showing that germline genomic variants also play an important role in the prognosis of children with neuroblastoma.

Just to give you a flavor of some of the different studies that have been performed, just looking at expression signatures in high risk patients. As you can see, there have been a number of studies that demonstrate that an expression signature can further refine classification for patients with high risk disease. So all these patients have high risk disease, but they do very differently depending upon whether they have a low versus high molecular risk signature.

One result of using genomic data for reclassification is that we're now slicing the pie, or the Bologna, into increasingly smaller pieces, as we define specific biologic subsets. And this makes it much more difficult to conduct clinical trials, because we have smaller and smaller populations of patients. We all know that research on small cohorts of patients is very difficult. And so the question is, how could we develop better treatments status strategies, and increased survival, and conduct studies on these cohorts as they continue to shrink?

And so one of the ways to think about solving this problem is obviously to increase collaboration. Increasing our understanding of the genomic drivers of neuroblastoma by linking genomic data that's been generated around the world with the phenotype data that we've collected in the INRG task force will be a very, very powerful way of further understanding what we can do to improve the outcome of children with neuroblastoma. And neuroblastoma data are currently isolated, and contained in silos, if you will.

So for example, there's an INRG data silo, where we have phenotype data, as I said, on 18,000 patients. There are also biobank silos in the Children's Oncology Group, and in Europe, and Japan, that have data on tumors that are banked. And then there are laboratories around the world that have done all these molecular studies. And there's omic data on all of these different tumors. But right now they're not connected. Now there's a huge challenge to share the data. It's cumbersome, and it's fraught with both technical, legal, and privacy issues. But we have to overcome these challenges so that we can improve our knowledge about neuroblastoma, and then subsequently develop better therapy.

So recently at the University of Chicago we've developed the interactive INRG database. And what we've done is we've transformed the current application that was housing the INRG data on these 18,000 patients, and we now have a web-based interface with an advance query engine, and technology that will facilitate linkage to other databases, both on and off site. And so that we now can link to omic data that's off site, perhaps, as well as biobank data.

So this is a diagram of the INRG database architecture. In the middle is the INRG patient data. And as you can see, we currently have links to establish to the COG nucleic acid bank, as well as the Children's Oncology bio tumor bank. These data can be accessed through an application server, and there can be a workstation either at a researcher's office, or also workstations at the statistician's office who help upload the data, and also help us analyze the data. We hope to soon be establishing additional links to European tissue biobanks, Japanese biobanks, and eventually we plan to link our INRG patient data to genomic data that we plan to upload in the Bionimbus protected data cloud that is currently coordinated by Doctor Bob Grossman, here at the University of Chicago.

The database infrastructure has been successfully established at the University of Chicago, and I'd like to credit Dr. Sam Volchenboum, who is our Chief Informatics Officer for the INRG task force. The front end of the web base has been built, and is designed to accommodate complex queries. Links have been established between the INRG database, and as I mentioned the COG biobank and the nucleic acid biobank. And the database currently contains information on 18,077 neuroblastoma patients.

We have updated followup data on the Children's Oncology Group patients, as well as we've added recently new fields, including race, ethnicity, sex, as well as the incidence of second cancers. European and Japanese colleagues have agreed to update followup data on the existing patients in the INRG database within the next couple months. And we also expect to be obtaining new patient data from these two groups in the next two years.

Just to give you an idea of what this database looks like, this is the query interface, where from your desktop computer you can log in and select the cohort of patients that you're interested in investigating, by selecting their age, or their stage, of whether they're N-myc amplified, et cetera. And this is what one of those queries looks like for patients who have, for example, Stage Four N-myc amplified disease. In this particular query there's a total of 1,342 patients that meet these criteria. And then you can see that we have 1,062 of these patients have tumor in the COG biobank. And there's also 815 of these patients that have tumor in the COG nucleic acid bank. So right from your desktop you can determine whether or not there are tissues available for you to do additional clinical trials.

So links to genomic data in the INRG database will provide unparalleled resource for advancing our knowledge of the epidemiology, pathogenesis, and genetics of neuroblastoma. And once again, I just want to emphasize there are strength in numbers. And analyzing large cohorts of patients will lead to more precise prognostication, the identification of new therapeutic targets, and ultimately more effective personalized therapeutic strategies for children with neuroblastoma.

And lastly I'd just like to acknowledge the INRG task force founding members, my COG colleagues, my colleagues at the University of Chicago who helped develop the INRG database, particularly Sam Volchenbaum, Chaim Kirby, and Robert Grossman, and also support that we received from the St Baldrick's Foundation, the Super Jake Foundation, the Children's Neuroblastoma Cancer Foundation, and the William Guy Forbeck Research Foundation. And then finally, but not last, of course, all our patients and families, who have been willing to participate on our very important clinical trials. Thank you.