How useful is genomic data in supporting advances in diagnosis, prognosis, and treatment selection? Genomic data have changed everything. When we started doing genetic analysis of childhood cancer, we were assessing single alterations with tools like PCR and Sanger sequencing because we didn’t have the knowledge or the technology to do anything more broadly. For example, when poor prognosis childhood neuroblastoma was linked to the amplification of a gene called MYCN, it quickly became obvious that we needed to develop an assay for that amplification. Test developers scrambled to create one (and succeeded) – but, of course, that was only one of multiple disease features we needed to examine. And so, for years, we kept developing one assay after another, each of which was critical to allocating patients to high- or low-risk treatment protocols, but none of which provided enough information in isolation. For example, patients with MYCN amplification may also have co-amplification of ALK for which we have targeted inhibitors – but with a single-gene MYCN copy number assay, you wouldn’t have that information.

The solution? A platform for all of the necessary analysis – MYCN copy number, c-Myc expression, and all of the unique features we find in childhood cancer. As we’ve discussed previously, childhood cancer is fundamentally different to cancer in adults – and a major factor affecting its accurate diagnosis is that we see different drivers, like copy number variation and chromosomal breaks. Chromosomal breaks and gene fusions are not easily detected by DNA sequencing; they can be seen much more readily at the RNA level. Ideally, a pediatric cancer panel should look at both RNA and DNA to detect the entire spectrum of common abnormalities in children. At the RNA level, it should detect gene fusions and expressed gene abnormalities; at the DNA level, copy number alterations and sequence abnormalities, including insertions and deletions (InDels). Next generation sequencing (NGS) platforms can look at both to spot multiple abnormalities in one large, comprehensive panel, so they have been a huge boon to diagnostic accuracy and treatment selection.

What can we achieve in the future by using this technology more broadly? Although pediatric oncologists and pathologists are a collaborative group, it can be very difficult to compare results when each physician performs different assays in different institutions in different ways with different content. One of the most significant opportunities offered by a standardized panel that incorporates the important features seen in childhood cancer is that, for the first time, no matter where you run the assay, you’ll get the same results – so, in theory, you can compare your data to that of someone at another institution or across the globe. This is essential for cancer in children, which is far less common than in adults. Learning what is and is not common – and, even more importantly, what is and is not clinically relevant – is correspondingly more difficult. NGS methods generate many candidate abnormalities, or variants of unknown significance (VUS), but knowing which ones matter is an ongoing challenge that can be met only by increasing our knowledge about which ones relate to disease onset, progression, treatment, or outcome.

“For the first time, no matter where you run the assay, you’ll get the same results.”

Science and medicine are moving ever more toward collaborative approaches and shared data, and standardized results (or “common data elements”) ensure that we’re all sharing the same information. At our institution we have implemented an NGS panel that has been an extraordinary success. Over 60 percent of the patients we examined (more than 200 in the past six months) had at least one actionable mutation – something nobody expected. Now, in addition to our conventional tumor board, we have a bi-weekly molecular tumor board in which we discuss an average of six to 10 patients and make treatment decisions based on the childhood cancer panel test results.

What distinguishes ICON from other databases? The biggest difference is that ICON is intended to be a clinically relevant, multiple-contributor, multiple-user, real-time database that contains both genomic and clinical data on the included patients. Many existing databases have very little clinical information linked to the genomic data, and each is focused on a specific type of tumor or tumors and a specific analysis platform. These can range from older microarrays to whole exome sequencing, commercial panels, or advanced research methods like epigenetic analysis of methylation, histone modifications, and the like. Although each is useful in its own right, none necessarily leads to direct clinical utility, in contrast, a comprehensive, all-inclusive database can at least document incidence and linkage to specific tumor types. When combined with a core database of specific genetic defects linked to specific patients, incorporating common data elements representing the content of the panel, it becomes possible to decide – for instance – whether or not a given VUS is likely clinically relevant. Alternative methods like statistical analysis of how often a given polymorphism occurs in a given population are useful guides, but fail to capture whether those variants are associated with disease. With larger numbers of cases, we acquire the power to decide based on statistical analysis linked to combined clinical and genomic data – a very powerful approach that is not possible without a database like ICON.

What can others join ICON? It’s easy – just contact Thermo Fisher Scientific and they will guide you. It only requires signing a simple document and using the standardized testing solution.