# Next Generation Sequencing Conversations...

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**NGS technologies are reaching a point of saturation with the majority of researchers using the Illumina platforms. Can you give us a short overview of where the NGS industry stands at the moment?**

Illumina technology is the current leader in the field, in particular when it come to whole genome sequencing. The HiSeq X Ten System has pushed the cost for a 30x human genome to less than $1000, but of course this is the cost for library preparation and sequencing consumables and does not include the cost of upfront sample preparation, staff and bioinformatics. High throughput has been one of the key drivers of Illumina in the research field, however in the clinical arena there are different factors affecting the decision on which platform to use, including the ability to use low input DNA, read length, speed, cost and flexibility. Other platforms, such as the Ion Torrent, are also being used in some clinical laboratories. The prediction is that we will observe a shift towards third generation sequencing technology in the next three years. The precision and the speed of single molecule sequencing are improving, and human whole genome sequencing might be possible soon using this technology.

**The majority of researchers are now working on the applications of NGS technologies for treating different diseases and genetic conditions. What challenges do you see researchers facing over the next few years?**

One of the main challenges that researchers will face in the next few years concerns functional analysis of the variants identified, in particular of mutations in non-coding regions of the genome. This will necessitate high throughput methods and systematic evaluation of functional consequences rather than the analysis of single variants individually. Another important challenge is the identification of druggable targets from the wealth of data (both DNA and RNA-based) generated using NGS technologies.

**At our 7th Annual Next Generation Sequencing Congress you will be addressing the 'Application Of Next Generation Sequencing To The Study Of The Molecular Pathogenesis Of The Myelodysplastic Syndromes' can you share with us a little background into the work that you are doing?**

The myelodysplastic syndromes (MDS) are clonal haematopoietic stem cell (HSC) malignancies showing frequent evolution to acute myeloid leukaemia (AML). There is a clinical need for new diagnostic and prognostic markers, and for more effective treatments in MDS. The molecular landscape of MDS has been greatly illuminated over recent years using NGS technology, including whole exome sequencing and targeted re-sequencing. Moreover, new biological insights into the pathogenesis of MDS have been gained from the analysis of RNA-sequencing datasets.

We have recently performed a comprehensive analysis to study the relationships between gene mutations in MDS, identified using targeted re-sequencing, and gene expression profiles in the HSCs from a large group of MDS patients. We deconvoluted the expression of genes into contributions stemming from genetic abnormalities, providing deep insights into how driver mutations affect the transcriptome, and ultimately clinical features and outcome.

The most frequent mutations found in MDS occur in splicing factor genes and emerging data suggest that these mutations result in aberrant pre-mRNA splicing. We are currently using RNA-sequencing to identify the key downstream targets of the splicing factor mutations in MDS. This work may lead to the identification of novel therapeutic targets in MDS.

The molecular events driving MDS progression to AML remain poorly understood. We have investigated the mutational status of a large group of MDS patients showing disease progression to AML by the study of serial samples using a NGS myeloid gene panel. We have determined the frequency and chronology of myeloid gene mutation acquisition during disease progression in MDS, identifying specific mutations that are associated with disease evolution, and illuminating the role of subclone development in MDS progression.

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### Career and Experience

Professor Jacqueline Boultwood obtained her PhD from the Department of Pathology, University of Wales College of Medicine in Cardiff, UK in 1988. She is now a Professor of Molecular Haematology and Director of the LLR Molecular Haematology Unit at the Nuffield Division of Clinical Laboratory Sciences, John Radcliffe Hospital, Oxford. Her research studies have primarily concerned the investigation of the molecular pathogenesis of the myelodysplastic syndromes (MDS), a heterogeneous group of myeloid malignancies. Her work has made a significant contribution to the determination of the molecular basis of several subtypes of MDS including the 5q- syndrome, alpha-thalassemia MDS and refractory anaemia with ring sideroblasts (RARS). Using next generation sequencing technology, she has further illuminated the molecular landscape of MDS, and provided new insights into the genetic basis of disease progression. Her teams study of the MDS transcriptome has yielded valuable insights into the pathophysiology and molecular pathogenesis of MDS, and has identified new prognostic markers for this disorder. Most recently her team has performed a comprehensive analysis to study the relationships between gene mutations, gene expression profiles and diagnostic clinical variables as well as outcome in MDS patients.