sought to extend our previous results on gene expression grade genes capturing mainly proliferation by adding into the model other relevant gene expression modules representing several biological processes in breast cancer such as estrogen receptor signaling and ERBB2. We sought to depict the connection between these modules and the previously reported molecular classification, several prognostic classifiers and the most established clinico-pathological variables. A number of interesting conclusions were drawn from this collaborative effort.
First, the disparity of the gene lists produced by several investigators can be attributed to heterogeneity in patient characteristics, expression profiling methodologies and sampling variation due to small sample size relative to the number of genes examined. Second, breast tumors were grouped into three main subtypes corresponding roughly to ER−/ERBB2−, ERBB2+ and ER+ tumors. Third, with respect to proliferation, both, ER−/ERBB2− and ERBB2+ subtypes were characterized by high proliferation, whereas the ER+ subtype appeared to be more heterogeneous. The latter was divided into two distinct subpopulations, the ER+/low and the ER+/high proliferation tumors resembling to luminal A and B subtypes respectively. Fourth, all previously reported prognostics signatures despite the disparity in their gene lists carry similar information with regards to prognostication. Fifth, proliferation genes appear to be the common driving force. Sixth, all these prognostic signatures are very useful for determining the risk of recurrence in the ER+ subgroup and less informative for ER− and ERBB2+ disease. Finally, nodal status and tumor size still retain important prognostic information.
Conclusions: This meta-analysis reveals for the first time connections between clinico-pathological traditional prognostic factors, expression-based sub-typing and prognostic signatures, highlighting the important role of proliferation in breast cancer prognosis.

S14

From gene expression signature to diagnostic test: Challenges in applying genomic technology to molecular diagnostics

J. Warrington. *Affymetrix Inc., USA*

Many exciting discoveries in cancer research have been reported using whole genome gene expression assays, yet few actual diagnostic tests have been developed and cleared for use in clinical practice. Successful adaptation of microarray technology into routine clinical practice requires establishing analytic reproducibility, consensus on quality, standard controls and best practice guidelines. Multiple international standards development efforts are underway that will accelerate acceptance and adoption of microarray technology in clinical studies, clinical trials and diagnostics. In this talk I will describe two recent initiatives aimed at addressing the first of many of the needs that must be resolved to fully realize the benefits of genome technology as well as provide an overview of the challenges and issues facing the development community.

S15

Interpretation of microarray data in cancer: a statistical viewpoint

S. Michiels. *Institute Gustave Roussy, Villejuif, France*

Introduction: Gene expression profiling is increasingly used in cancer research. The main objectives of microarray studies are (1) to identify homogeneous subtypes of a disease on the basis of gene expression, or (2) to find genes that are differentially expressed in tumours with different characteristics, or (3) to develop a rule on the basis of gene expression allowing the prediction of patient prognosis or of the response to a particular treatment.
Main message: Using pioneering work on breast cancer as an example, I shall review some of the problems in interpreting the results of these types of study, and discuss the statistical power, the validity and the clinical usefulness of the findings.
Conclusion: The example of breast cancer illustrates a problem that is central to the interpretation of microarray data. The hypothesis underlying each study should be stated clearly and the primary objective of a study should aim at its rejection. Studies with a solid experimental design and larger sample sizes are required before gene expression profiling can be used in the clinic to predict outcome.

S16

Tumor biomarkers, the need for a new way to conduct business. Perspective from the US FDA

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Introduction: Despite of major advances in biotechnology and life sciences, new drugs applications to US FDA are not increasing and clinical research and the process of development is getting longer and more expensive. Furthermore, the predictability of drugs entering clinical trials to reach the market is shrinking.
Main Message: We are currently using tools of the 1960's and 1970's for the science of the 21st century. We are conducting clinical trials with designs intended to avoid bias of variability in an age where variability is at the heart of personalized medicine.
Conclusions: A paradigm shift in the way we do business in drug development from early discovery to clinical trial design has to be implemented and a concerted effort of all stake-holders is needed for a new way we do business.

S17

Epigenetic biomarkers in human cancer

M. Esteller. *Spanish National Cancer Centre (CNIO), Madrid, Spain*

Introduction: Recent years have seen the mapping of increasing numbers of genes in which promoter CpG islands are hypermethylated in cancer.
Main Message: Such DNA-methylation mapping has revealed unique profiles of hypermethylated CpG islands