GENOMICS INFORMATICS PROTEOMICS METABOLOMICS

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The Agilent Microarray Platform and the Microarray Quality Control (MAQC) Consortium Study

The Microarray Quality Control (MAQC) Consortium recently published findings of the largest collaborative study to date on microarray performance and cross-platform comparability. This study was led by FDA scientists and involved more than 600 hybridizations across seven platforms including 137 participants from 51 organizations[1].

The first study of its kind, the MAQC Consortium study looked at the concordance between microarray platform technologies and orthogonal techniques, and highlighted the key technical performance and data processing attributes that should be considered when evaluating the design and results of microarray experiments. The capability of the Agilent microarray platform has been clearly demonstrated in this highly anticipated study.

In this MAQC study overview, we discuss Agilent's platform performance in the core areas of sensitivity and accuracy, and describe how they relate to data variance. Additionally, we highlight some factors that should be considered when processing data to achieve the best overall performance in measuring gene expression.

Superior Sensitivity and Accuracy

Today, many scientists employ gene expression profiling to search for novel pathways and to discover new biomarkers associated with specific biological conditions. These experimental goals require that researchers use technologies that enable the repeated detection of biomarker candidates with a high degree of sensitivity and accuracy. The MAQC study clearly demonstrated that Agilent's microarray platform is the most effective for this type of work. Agilent test sites consistently detected more differentially expressed genes with the highest accuracy (Figures 1 and 2).

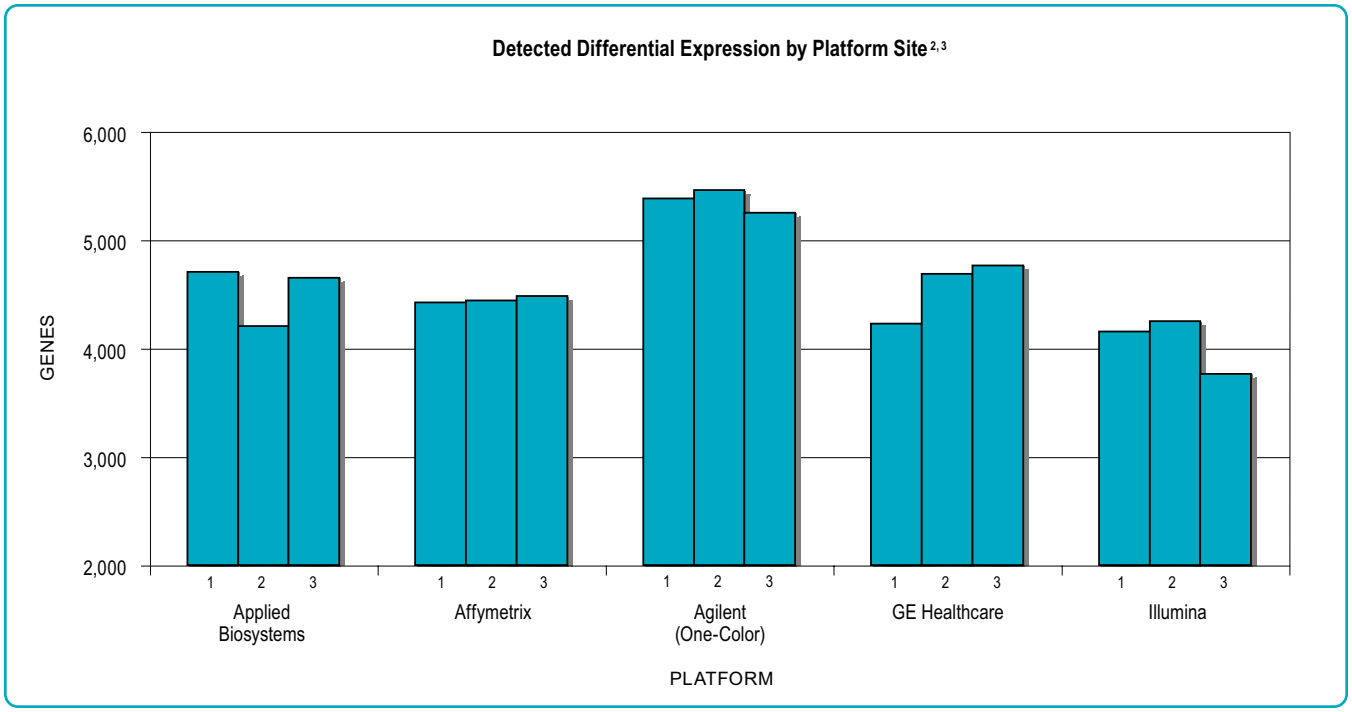

Figure 1. Detected differential expression by platform site
Agilent's whole genome microarrays have been designed to maximize detection of differential expression. Every Agilent test site detected more differential expression than any other platform site.

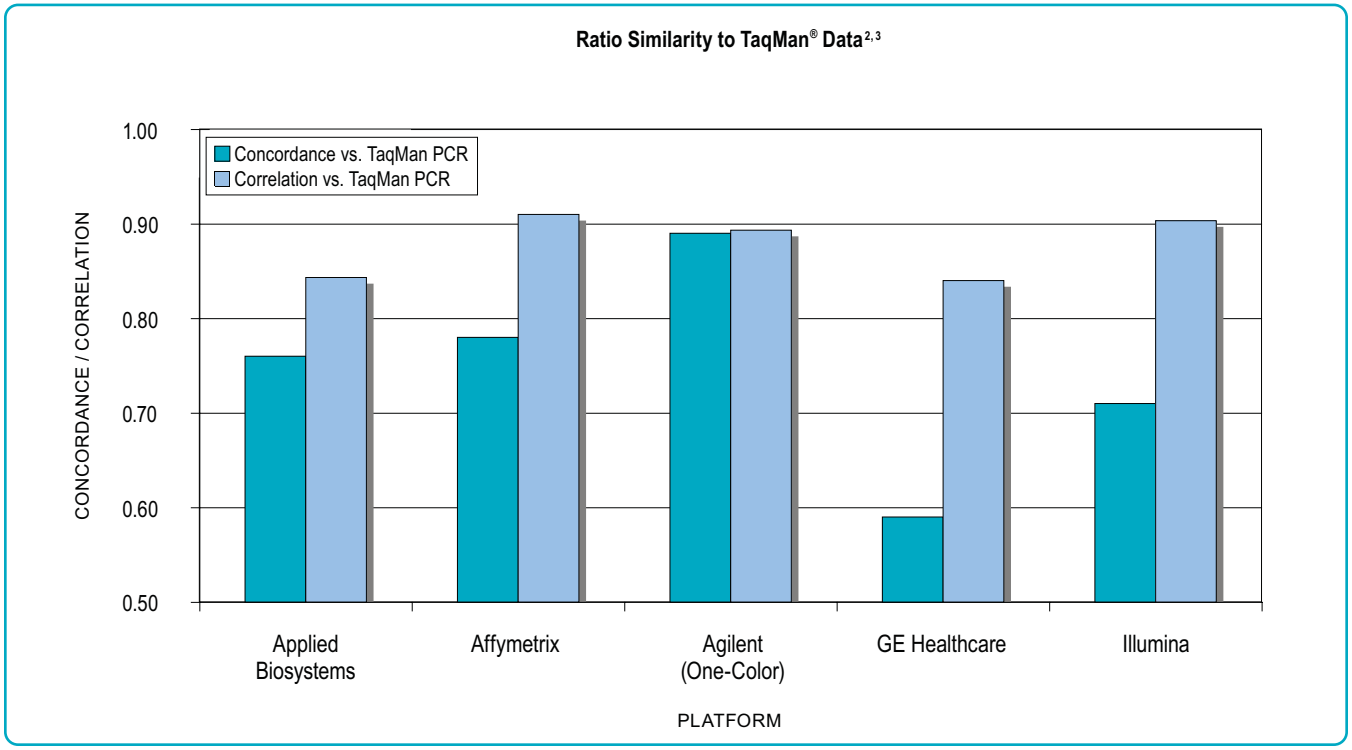

Figure 2. Ratio similarity to TaqMan® real-time PCR assay
Accurate detection of differential expression is measured by concordance (slope or compression effect) and correlation (tightness of scatter) to an orthogonal gold-standard method. The Agilent microarray platform clearly exhibits the best relationship to the TaqMan® assay amongst the platforms tested. Ideal result is a value of 1.00 for both concordance and correlation.

Optimized Design

Agilent has made a number of customer prompted design choices in developing its microarray platform, the results of which are evident in the MAQC study. The most crucial and differentiating of these choices are:

- An empirical probe selection process, enabled by our flexible *in situ* array production process, which identified the most responsive and specific probes for each target sequence.
- The use of a high-stringency microarray processing protocol, which prevents non-specific hybridization from compromising probe response.
- The development and use of background subtraction algorithms that effectively remove background signal that would lead to data compression, and thus decreased sensitivity and accuracy.
- The employment of a simple scaling normalization procedure that does not add a constant to the signal intensities (variance stabilization) and does not force disparate samples to the same artificial signal distribution (quantile normalization).

These platform design choices, in combination with the benefits of our high-quality 60-mer probes, lead to exceptional accuracy and sensitivity. As a consequence of this design strategy, the total platform coefficient of variance (CV) is not as compressed as other platforms, which was demonstrated in the MAQC study.

The members of the MAQC consortium were diligent in describing the effect that CV reduction by data processing could have on platform performance.[4, 5]

When considering various methods for processing microarray data, it is critical that users understand each method's impact on platform performance with respect to sensitivity, accuracy and variance.

Conclusions

The MAQC Consortium has broken new ground in its objective evaluation of microarray technologies and has reached a level of consensus on how to properly compare data generated in microarray experiments.

As with any thorough scientific endeavor, new questions have emerged that require additional consideration by the community. Some of these questions revolve around the appropriate application of data processing techniques with the goal of improving overall data quality.

It is Agilent's position that the best way to achieve ever higher sensitivity, accuracy and reproducibility in microarray technology is through an integrated approach to improved overall assay performance. Some of the critical factors in achieving this goal are high manufacturing quality, robust methodologies, reliable signal detection and comprehensive workflow quality control. These important platform attributes can be seen in both Agilent's MAQC microarray performance and in Agilent's newly available microarray products.*

In the MAQC study, Agilent has presented a technology platform and interpretive principles that well represent the needs of our customers and the community at large. In the end, a balanced approach to system optimization will yield the most valuable and complete picture of the scientist's research goals.

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*Since the completion of the microarray hybridizations performed for the MAQC, Agilent has launched a new line of lower-cost and higher-performing gene expression microarrays. In the spirit of the MAQC study, we have run the new arrays with the same reference samples that were presented in the study. For a poster of the results please go to: http://www.opengenomics.com/MAQC

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