

# Executive Summary

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The term “translational medicine” seems to have become the latest buzz word in the health care industry; however, a simplified version of its philosophy has always been in use. The ability to look at the cause and effect of administering a treatment seems to be inherent, and the next logical step is to tweak that treatment based on the outcome. Translational medicine of today is obviously much more complicated. Researchers in the pharmaceutical and biotechnology arenas are using the concept of translational medicine to find ways to discover new medications, tweak backup compounds, determine dosing strategies, and minimize adverse events and increase safety, all while trying to decrease the time to market. They are also hoping that translational research will save research funds by discovering at an earlier stage if a compound will not survive, thereby decreasing attrition. Translational medicine can also help with patient stratification. Assay technologies can be used to determine if patients will respond to a particular therapy or if they may have an adverse reaction to a certain medication.

Translational medicine is not a 1-way street. Researchers gain the most information both by looking at the information coming from discovery to bring a compound into clinical trials and using the information from those trials (and even after the product is marketed) to better understand the underlying disease state and the pharmacokinetics/pharmacodynamics of the drug or to assist in creating the second generation of that therapeutic.

The goal of translational medicine is to discover new ways to provide the best in patient care, whether it is from studies aimed at understanding human pathology or experiments to create new, novel therapeutics.

## History of Assay Technologies

Assay technologies have been evolving since scientists first discovered that they could measure glucose, insulin, and several hormones in the blood to help them diagnose disease. Early instruments such as the Ames Reflectance Meter, used for detecting glucose levels, have morphed into such sophisticated systems as flow cytometers. The Human Genome Project provided the basics for researchers to launch into the field of human genomics, and they needed the tools to accomplish this. DNA microarrays allowed for massively parallel gene expression analyses. However, scientists soon discovered that, although the genome-wide assays were extremely valuable, there were genes of interest that they had difficulty measuring when they got hundreds of data points from a microarray. Low- to mid-density assays have allowed scientists to pinpoint the genetic code for a variety of uses, from genetic heredity studies to drug metabolism and patient stratification.

## Multiplex Assays in Translational Medicine

### Products and Applications

Chapter 3 of this report looks at several different classes of assay technologies that fit into the low- to mid-density paradigm. Microarrays, such as Affymetrix's GeneChip, have been modified so that specific genetic markers can be examined, as in the case of the AmpliChip Leukemia Test, CYP450 Test, and p53 Test. The MammaPrint breast cancer prognosis test from Agendia (Amsterdam, The Netherlands) was the first cleared-for-marketing in vitro diagnostic multivariate index assay (IVDMIA) device to be used on freshly frozen tumor tissue. Extension arrays are being used in technologies such as Asper Biotech's (Tartu, Estonia) APEX (arrayed primer extension). Several companies, such as Osmetech and Randox, generate low-level multiplex assay products based on positional DNA microarray technology. Xceed Molecular (Toronto, Ontario, Canada) and PamGene (The Netherlands) both emphasize diagnostic applications and offer products for low-level multiplexing based on positional microarray technology featuring flow-through characteristics. Encoded bead arrays provide improved binding kinetics that offer great flexibility in the creation of the assay. Beads can be color-encoded, bar-coded, or sequence-coded. Luminex's xMAP color-encoded set of 100 beads has been incorporated by a number of companies, such as Panomics (Fremont, CA), into their diagnostic or research multiplex assay products. Polymerase chain reaction (PCR)-based technologies are examined, including those offered by Applied Biosystems (Foster City, CA), Epigenomics (Berlin, Germany), Gene Express (Toledo, OH), Genomic Health (Redwood

City, CA), and OncoMethylome Sciences. Protein array technologies have the capability to screen thousands of interactions, including protein-antibody, protein-protein, protein-ligand, or protein-drug; enzyme-substrate screening; and multianalyte diagnostic assays.

Two case studies are presented in Chapter 4 that demonstrate how translational medicine is used in medicine today. The first is the discovery of a panel of biomarkers that identify ovarian cancer in the early stages of the disease, when the chances of treatment are greatest. The second example demonstrates how a group of researchers used Gene Express' *StaRT*-PCR to identify responders to cisplatin chemotherapy.

### Future Directions

The obvious next step for these assay technologies will be improvement: very high sensitivity and specificity, the ability to detect biomarkers from a small sample, and smaller instruments that can translate into diagnostic devices. Sample preparation and size were cited during the online survey conducted by Cambridge Healthtech Institute (CHI) as one area that needed improvement. The ideal diagnostic tool would be inexpensive, efficient, easy to operate and interpret, accurate, and available to diagnosticians. In the field of proteomics, new technologies will need to be discovered to enable these disciplines to catch up to the information available with genetics. One hope is that these mid-density multiplex assays will have an impact on the cost of healthcare by enabling the diagnosis of disease earlier and faster, and by helping pharmaceutical and biotechnical companies to decrease costs by bringing products to market faster.

### FDA Perspective

The FDA has put forth the Critical Path Initiative (CPI) as “a vision statement to improve the efficiency of product development industry-wide and to identify and prioritize (1) the most pressing development problems for new drugs and other therapeutic agents and (2) the areas that provide the greatest opportunities for rapid improvement and public health benefits.” Several activities under the umbrella of the CPI, such as the Oncology Biomarker Qualification Initiative (OBQI), were initiated to improve the clinical utility of biomarker technologies as diagnostic and assessment tools that facilitate the development of safer and more effective cancer therapies. Issues such as the validation of assay technologies and qualifications of biomarkers are high priorities of these initiatives.

## **Industry Opinion**

The report concludes with industry opinions concerning current views and practices in the field. These are presented in the form of in-depth interviews with experts in both translational medicine and specific assay technologies and in results gleaned from a small online survey of life science researchers who use low- or medium-density arrays in translational medicine.