The 2014 European Summit on Biomarkers: Biomarkers in Diagnostics

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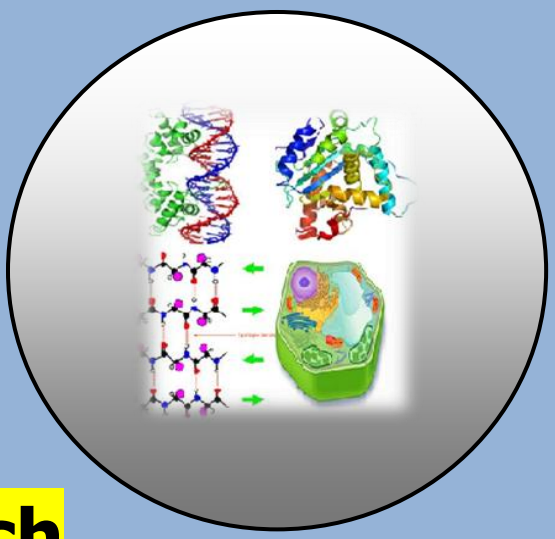

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REVIEW ARTICLE

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The 2014 European Summit on Biomarkers: Biomarkers in Diagnostics

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ABSTRACT

Biomarkers hold promise in medicine, e.g., the ability to use minimally non-invasive bloodwork to improve screening, increasing the accuracy of diagnosis, and to monitor disease progression or regression are amongst the goals of biomarker development. The 2014 European Summit on Biomarkers highlighted many presentations featuring groundbreaking research that may provide future progress. This article is a summary of most of these presentations and a brief review of some of the supporting articles that were deemed relevant. In addition, this article should provide all medical providers and clinical researchers with updates from the 2014 European Summit on Biomarkers with a focus on biomarkers in diagnostics.

Keywords: European Summit on Biomarkers, Personalized Medicine, Biomarkers

INTRODUCTION

This is a report on the *3rd Biomarkers in Diagnostics Conference*, part of the *2014 European Summit on Biomarkers*, which was hosted by the conference production company *Global Technologies Community* (GTC), October 9th& 10th, 2014. The event was located at the beautiful and luxurious Ballsbridge Hotel, Dublin, Ireland.

A biomarker is a quantifiable material in an organism whose presence is suggestive of some phenomenon, e.g., disease (Biomarkers Definition Working Group 2001). The discovery of clinically significant biomarkers is becoming increasingly significant to predictive, preventative, and personalized medicine. Establishing a repertoire of biomarkers from various etiological disease pathways has the potential to provide clinicians and researchers with objective laboratory-based data. This information can improve and compliment the value of the subjective symptoms that are reported by the patient, i.e., it gives an objective indication of the medical state observed from outside the patient (Strimbu and Tavel 2010).

In addition, biomarkers can assist in the elimination of differential diagnoses that are initially formulated and improve the accuracy of the diagnosis. Finally, biomarkers can be powerful tools in providing more detailed information about the prognosis andthe success, or failure, of different treatment regimens.

The utilization of biomarkers is pivotal to making the concept of personalized medicine a reality. Personalized medicine requires the ability to use biomarkers that signal disease risk or presence before clinical signs and symptoms emerge. In this way preventative medicine offers the opportunity to focus on prevention and early intervention rather than on reaction at advanced stages of disease (Personalized Medicine Coalition 2014).Additionally, preventative medicine can direct the selection of optimal therapy, reduce trail-and-error prescribing, help avoid adverse drug reactions, increase patient adherence to treatment, improve quality of life, reveal additional/alternative uses for medicine/drug candidates, and help control the overall cost of health care.

The initial portion of the conference had five featured speakers whose focus was primarily on the value assessment of biomarkers in research and drug development. Other portions of the conference focused on predictive verse prognostic biomarkers in personalized medicine, new diagnostic biomarkers & their development (which was separated into two parts on day one and two of the conference), and prospects of systems medicine in personalized medicine. There were poster presentations at the end of the first day of the conference and a general session at the end of the final day of the conference.

Health Economics Value of Biomarkers and Reimbursement Environment

One of the main hopes is that biomarkers will provide a minimally invasive technology for individual patient profiling, disease monitoring, and disease management. Patricia McLoughlin, Director Companion Diagnostic Partnerships, Global Business Development, QIAGEN, proposed that liquid biopsies are potential target biomarkers for lung cancer. The three major domains of a liquid biopsy are:

1) Free circulating nucleic acids- this consists of protein bound DNA or small RNA
2) Exosomes- these are small vesicles containing DNA or RNA
3) Circulating tumor cells- cancer cells that are released from the tumor

Citingrecent research on lung cancer, Patricia McLoughlin demonstrated that multi-modal testing with liquid biopsy can be used as a companion diagnostic tool for treatment decisions and can also be utilized as a monitoring tool during treatment. This translates into new options for the patient and market access for new therapies. Current activity in this area includes the collaboration between AstraZeneca and QIAGEN to develop diagnostic test for lung cancer patients suitable for treatment with IRESSA (Gefitinib). IRESSA is an oral first-line treatment for epidermal growth factor receptor (EGFR) mutation positive non-small cell lung cancer. IRESSA monotherapy has shown greater progression-free survival, improved tolerability, and increased quality of life when compared to the doublet chemotherapy carboplatin/paclitaxel (Thongprasert et al. 2011; Mok et al. 2009).

Much thought, planning, and assessment goes into establishing the success and impact that biomarkers may have. In the early clinical development of biomarkers there are five main core biomarker platforms: flow cytometry, histochemistry, molecular assays, pharmogenetics, and immunochemistry. After development, value assessment requires biomarker data generation, which includes levels of validation, fit for purpose, and eventually one repository to record the outcomes from all biomarker studies.

One such system was discussed by Michael Burzynski, executive director, Biomarker Technologies, Clinical Biomarkers, ECTR, Bristol-Myers Squibb; called Biomarker Strategies, Assay Deliverables, Biomarker Analysis Requests (BASAR). This system breaks up the biomarker program into one of three categories: pharmacodynamics effect, target engagement, and predictive biomarkers- each has a strategic plan that determines how the assay is deliverable; e.g., mRNA levels, cytokine levels, receptor occupancy, genetic variant, or target expression. The assay deliverable produces a BASAR request of common and uncommon biomarker platforms, and then the value is determined by success and impact, i.e., whether the biomarker study was successfully executed, irrespective of the outcome of the data and/or interpretation, and whether the biomarker study provided meaningful data/information upon which one or more decisions could be made, respectively. Consequently, the BASAR system enables scientists to formally communicate biomarker strategy and execution plans.

Another way of determining the value of a biomarker is to look at the payer's expectations and requirements. This was highlighted by Meridith Johnson, director, Health Economics and Outcomes Research, GE Healthcare; who elucidated the importance of demonstrating the value of biomarkers as to what evidence payers will require. This will differ between regulators. In addition, Meridith Johnson stressed the importance of payer evaluations of evidence feedback and how pay perspectives should be incorporated into product development. This could include narrowing down the patient population that will benefit from that particular biomarker. Hence, ignoring the payer's needs will ultimately affect the uptake and sales of any biomarker.

The topic of personalized medicine was frequently discussed at this conference. Personalized medicine value is price sensitive. If biomarker treatment is personalized a target population that will benefit becomes smaller. This was highlighted by Joachim Greuel, Managing Director & Co-Founder, Bioscience Valuation, as he proposed that non-personalized drugs in development have limited financial value and demonstrate a decrease in profit. Whereas, personalized drugs may offer higher values by predicting the patient population likely to respond. Therefore, personalized medicine can potentially be more efficient and safer with higher market share within the target group. Joachim Greuel mentioned *The Economics of Personalized Medicine Initiative*. This proposal seeks to do four things:

1) Assess the economic incentives of all relevant stakeholders to support or not support personalized medicine
2) Provide meta-analyses of available research, stakeholder interviews, and quantitative economic modeling
3) To demonstrate the value of personalized medicine to patients and society
4) To show the financial value to developers and marketers of therapies and diagnostic tests.

Joachim Greuel also pointed out that the cost of screening for the target patient group must be taken under consideration. This was supported by another group testing the cost effectiveness of screening among lung cancer patients with drug sensitivity markers (Atherly and Camidge 2012). This study did suggest that cheaper screening tests that miss some true positives can be more cost-effective if proportional reductions in cost exceed the proportion of subjects missed. However, no general consensus in the literature can be found for the general support or opposition of this suggestion.

Franz Hessel, Professor for Healthcare Management, SRH University Berlin, discussed genetic markers in the treatment of cancer. Biomarkers can genetically stratify therapy and tests results can assist in selecting therapy for responders and non-responders, identify patients with high risk of severe adverse events, identify subgroups at risk for disease progression, and monitor drug therapy success and drug dosage. Although, genetic biomarkers possess the ability to genetically stratify treatments, this is rarely black and white. Franz Hessel also suggests that the commercialization of genetic biomarker tests for the use in oncology as well as in the evaluation of the clinical benefit of personalized medicine technologies has become an essential part of oncology. However, there are three main hurdles for entering the market:

1) Approval- can the technology be used?
2) Market penetration- will the technology be used?
3) Reimbursement- will the technology be reimbursed when used?

Franz Hessel proposed that Health Economics Outcomes Research (HEOR) studies may help for personalized medicine technology, biomarker tests, and test strategies by helping to demonstrate the benefit to the payer. HEOR is a regulation which is utilized to complement traditional clinical development information (Holtorf et al. 2012). This includes efficacy, safety, and quality. This information guides decision makers regarding patient access to specific drugs and services.

Predictive Verse Prognostic Biomarkers in Personalized Medicine

In the next section of the conference predictive and prognostic values were evaluated in the area of cardiac transplantation, Huntington's disease, and multiple myeloma. A predictive factor is a clinical or biological characteristic that provides information on the likely benefit from treatment in terms of survival and improvement in the disease state (Italiano 2011). Whereas, a prognostic factor is a clinical or biological characteristic that provides information on the likely outcome of a disease in an untreated patient (Italiano 2011). In terms of biomarkers in personalized medicine, utility ultimately depends on the intended use, i.e., whether it is predictive or prognostic.

Tissue rejection is a large contributor to morbidity and mortality after heart transplantation. The current gold standard diagnostic for acute rejection is to monitor with repeated tissue biopsies which are highly invasive procedures and have associated risks (Liu and Baughman 2011):

1) Blood clots
2) Bleeding from the biopsy site
3) Cardiac arrhythmias
4) Infection
5) Injury to the recurrent laryngeal nerve
6) Injury to the vein or artery
7) Pneumothorax
8) Rupture of the heart
9) Tricuspid regurgitation

These underlying risksfashion the need for imperative biomarkers to non-invasively predict acute cardiac rejection. Robert McMaster, Professor and Associate Dean of Research, University of British Columbia, proposed that the future diagnosis of cardiac transplant rejection will include both genomic and proteomic biomarkers.

In his previous research, it was demonstrated that a predictive biomarker panel that contained both genes from the recipient's whole blood (an 18 probe subset) and donor myocardial tissue (a 25 probe subset) provided clinically relevant predictive power and may assist in personalized immunosuppressive treatment and rejection monitoring (Hollander et al. 2013). At a previous conference, *The 5th International Conference on Biomarkers and Clinical Research* (OMICS Group Conferences), Robert McMaster discussed a panel of 10 genes and 6 plasma protein biomarkers that demonstrated 100% sensitivity and 96% specificity in detecting acute heart allograft rejection.

Huntington's disease (HD) is a neurodegenerative, movement, and mood disorder which is caused by the production of a mutant protein called huntingtin protein (HTT). Symptoms include motor abnormalities (e.g. chorea), cognitive decline, and psychiatric disturbances. At the present time there are no disease-modifying therapies for this disease. Currently, treatment targets solely on symptom management. In a review of therapeutic interventions for disease progression in HD it was concluded that further trials with greater methodological quality can be piloted using more sensitive biological markers (Mestre et al. 2009).

Cristina Sampaio, Chief Clinical Officer, CHDI Foundation, in current research suggests that HTT chromosome 15 mutations and HTT protein may be potential biomarker targets. In a supporting study, a development using quantification assays for HTT provided a panel of detection assays for soluble polyglutamine-expanded (mutant) and total (polyglutamine-independent) human HTT and rodent HTT protein (Macdonald et al. 2014). This assay was able to selectively measure the amount of soluble HTT protein in a variety of biological samples. The ability to quantitatively compare the amount of HTT protein will stipulate guidance for dose selection during treatment. It will also provide the ability to monitor the pharmacodynamics effects of molecular therapies, as well as other approaches that modulate the levels of HTT protein. Cristina Sampaio concluded that there is a need to better understand what is being measured which in turn will enable medical providers to make clinically meaningful decisions based on this assay in the context of a clinical trial.

Pertinent to HD research, Cristina Sampaio and group recently reviewed major landmarks in clinical development (Sampiao et al. 2014). With specific regards to biomarkers, it was concluded that TRACK-HD and PREDICT-HD have both engendered significant evidence to support their use in novel outcome measures for HD clinical trials, e.g., volumetric imaging, quantitative motor (Q-motor) measures, and cognitive endpoints.

Multiple myeloma (MM) is a cancer of the white blood cells called plasma cells. It is the second most common blood cancer. Treatments consist of chemotherapy, radiation, stem cell transplant, surgery, bisphosphonates, and plasmapheresis (the removal, treatment, and return of blood plasma). Developing accurate methods that measure response to treatment and survival are of significant importance.

Scott Ely, Associate Professor, Clinical Pathology and Laboratory Medicine, Weill Medical College of Cornell University, discussed using plasma cell labeling index and multiplex staining (immunohisto chemistry) to observe cancer cells and proliferating cells which can be used together to monitor MM with more accuracy. A multiplex assay is a method that simultaneously measures multiple analytes; as opposed to only one, during a single cycle.

Plasma cell labeling index is a method that measures plasma cell proliferation and is an important prognostic factor in diagnosing MM (Greipp and Kumar 2005). The ring-dot method is clinically validated as Ki67/CD138 correlates with survival. Scott Ely's group developed a ring-dot IHC which was created to make it easier for pathologists to use imaging. A newer method, the purple method, has also been developed which makes use of two stains (a membrane and a nuclear stain) to localize structure in the same cell.

Scott Ely was also involved in a recent study identifying and characterizing a subset of IgG4-secreting myelomas (Geyer et al. 2014). These findings suggested that an increase in the number of IgG4-positive plasma cells is not a chief etiological agent in IgG4-related diseases. In addition, it was suggested that elevated serum levels of IgG4 is not adequate to generate the typical disease presentation and is not considered diagnostic.

New Diagnostic Biomarkers & Their Development: Part I

The topics of the next section of this conference focused on the diagnostic utility that biomarkers will potentially incorporate in medicine. Diagnosing and early detection of disease is important because it increases patient survival, especially in oncology. Keep in mind that the global prevalence of cancer has increased from 12.7 million in 2008, to 14.1 million in 2012, and is projected to rise to 25 million by 2034 (Steward and Wild 2014). The presentations in this section focused on diagnostic and early detection biomarkers for cancer.

Wendy Alderton, Chief Scientific Officer, Abcodia, discussed some of the challenges in developing biomarkers for the screening and detection of early cancer. One challenge is the cancer screening market. There is a large market for population screening but a high barrier to enter into the market for use. This is primarily due to the cost of expensive and lengthy prospective trials. Consequently, this results in low profit margins. A second challenge is the economics of the screening, i.e., the screening must result in improvement in patient outcome in order to be deemed useful. However, the performance and specificity of biomarkers can produce false positives, which can result in over-diagnosis, increased costs due to secondary follow up, and inflicting anxiety unnecessarily on individuals without cancer.

Wendy Alderton also discussed an epigenomic biomarker- Epi proColon, for colon cancer screening. This was approved for use by the FDA in March 2014 by a narrow margin (Brown 2014). Epi pro Colon is a qualitative test to detect methylated Septin 9 DNA, which has been associated with colorectal cancer, and is a specific and sensitive blood test (Warren et al. 2011). In terms of improvement in patient outcome, one epidemiological study demonstrated that methylated Septin 9 DNA testing decreased colorectal cancer mortality by 53-61% (Ladabaum et al. 2013). It has been proposed that Epi proColon may someday replace the current and very invasive gold standard for screening for colorectal cancer- the colonoscopy.

Additionally, Wendy Alderton discussed a promising new test for ovarian cancer called risk of ovarian cancer algorithm (ROCA). This is a computer process which will have mortality data published sometime in 2015. This study followed changes in tumor marker CA125 in three risk groups- low, intermediate, and high; and then ROCA calculated the risk verse the benefit for the subjects screened for ovarian cancer.

Caroline Chapman, Associate Professor, Tumor Immunology, The University of Nottingham, discussed the use of auto antibodies as biomarkers in cancer detection.

Immuno-editing is a dynamicmethod that entails immuno-surveillance and tumor progression, which consists of three phases- elimination, equilibrium, and escape (Dunn et al. 2004). A recent review proposed that new immunomodulatory agents, specifically anti-CTLA4 and anti-PD1/PDL1 monoclonal antibodies have shown impressive results in efficacy and tolerability in lung cancer, which has led to several large randomized phase III trials (Rolfo et al. 2014). Caroline Chapman did point out that although immuno-editing shows promise it must be kept in mind that screening modalities yield a high number of false positives.

Prostate cancer is the second most common cause of death in males in the U.S. (Steward and Wild 2014). This is usually detected in the clinic by an invasive digital rectal exam and annual screening with a blood test for prostate specific antigen (PSA). Benign prostatic hypertrophy (BPH) can also cause an elevation in PSA, mimicking prostate cancer. Differentiation between the two is confirmed with a highly invasive prostate biopsy. Consequently, the development of a non-invasive means of confirming the differentiation between prostate cancer verses BPH would have high utility in the clinic and significantly reduce the amount of unnecessary prostate biopsies.

Markus Beier, Vice President Strategy and IP, Comprehensive Biomarker Center, discussed the use of microRNA (miRNA) biomarkers for the non-invasive diagnosis of prostate cancer. Approximately 0.0001% of the human genome expresses miRNA. These are small molecules that range between 15-27 base pairs and they regulate gene expression (Ambros 2004; Bartel 2004). As biomarkers, miRNA does correlate with physiological changes in tissue, body fluid, and is found in the bloodstream. This makes it a good therapeutic and diagnostic agent as miRNA is highly stable and sufficiently concentrated enough for detection on microarray and next generation sequencing (Kuner et al. 2013).

Markus Beier pointed out that miRNA can differentiate between prostate cancer and BPH. This is clinically useful as it may negate the need for invasive prostate biopsies. In addition, Markus Beier mentioned that miRNA can be used to monitor tumor progression in prostate cancer. This has been proven with miRNA-375 and miRNA-141, as their expression has been found to be enhanced in prostate cancer specimens, their release into the blood is associated with advanced cancer disease, and their levels are also well correlated with high Gleason scores/lymph-node positive status in second independent validation studies (Brase et al. 2011).

Daniel Chelsky, Chief Scientific Officer, Caprion Proteomics, discussed mass spectrometry technical approaches and targeted multiplexed assays- a multiple reaction monitoring (MRM) analysis in Alzheimer disease (AD) and lung nodule diagnostic testing. It was previously confirmed that heart fatty acid binding protein (HFABP) is associated as a putative marker for dementia disorders, e.g., AD (Chiasserini et al. 2010). Daniel Chelsky reported an assembled 142 protein assay specific to AD and national death index (NDI), that 5 proteins and beta-amyloid/p-tau (+/- age, gender) had the most accurate pharmacokinetics (AUC: 0.80) to predict which patients will convert from mild cognitive disorder to AD. In addition, a recent study using a targeted proteomics approach confirmed that 4 CSF markers: amyloid precursor protein, neuronal pentraxin receptor, NrCAM, and Chromogranin can potentially be used as disease progression markers (Wildsmith et al. 2014).

Daniel Chelsky also discussed biomarker diagnostic tests that were based on a large scale MRM study design, which was able to distinguish between benign and malignant pulmonary nodules. Using mass spectrometry, this study identified 13 protein classifiers of benign verse malignant nodules, which were independent of risk factors, e.g., age, nodule size, or the number of pack-years of smoking. This type of test allows the clinical and economic opportunity to categorize a large number of over-treated benign nodules.

Prospects of Systems Medicine in Personalized Medicine

This section of the conference focused on risk-benefit and management in the development and impact of biomarkers in preventative medicine. Scott Marshall, Managing Director of Precision Analytics, Precision for Medicine, discussed the importance of empirical evidence and risk-benefit and management in developing biomarkers. It was demonstrated that a 140% improvement was made by incorporating biomarkers in a recent study on non-small cell lung cancer (unpublished results). The importance of drug-diagnostic (Rx-Dx) development pathway is becoming critical to the success of drug development, which means that precision guided therapeutics will drive the future of drug development. This includes four main biomarker strategies in the era of personalized medicine:

1) Market differentiation strategy to increase uptake
2) Evaluation of safety profiles
3) Patient selection strategies for efficient trail designs
4) Speed the path to the market and regulatory approval

Edward Blair, Managing Director, Integrated Medicines, discussed the impact of biomarkers and companion diagnostics on the BioPharma Sector 2025. He pointed out that one of the key trends in therapeutic areas is the chronic disease opportunities remain while pharma expands into diseases with fewer treatments. However, with chronic diseases early detection, diagnosis, and effective treatment is important because of the correlation to a better long-term outcome for the patient.

Poster Presentations

There were several poster presentations at the end of the first day of this conference during the evening networking reception. One of the standout poster presentations was displayed by Michael Lamar Seibenhener, Research Associate, Department of Biological Sciences, Auburn University. In previous research Michael Lamar Seibenhener and group demonstrated that p62 is localized to mitochondria in non-stressed situations and deficiency in p62 impairs defects in mitochondrial membrane potential, which results in mitochondrial dysfunction (Seibenhener and Zhao et al. 2013). In this study, mitochondrial function was restored when p62 was returned. In the poster presentation newer research was presented by Michael Lamar Seibenhener and group which demonstrated that the over expression of SQSTM1/p62 increased mitochondrial energy output and improved transcription factor import into the mitochondrial matrix (Seibenhener and Du et al. 2013). These results were obtained using transgenic mice over expressing SQSTM1/p62 (or single point mutation p3921 in UBA domain of SQSTM1/p62). The over expressing of SQSTM1/p62 resulted in elevated levels of mitochondrial functionality which was correlated directly with discernible improvements in mouse behaviors in regards to affective spectrum and anxiety disorder, as well as improved spatial learning and long-term memory formation.

New Diagnostic Biomarkers & Their Development: Part II

This section was the second part of new diagnostics biomarkers and their development that was held on day one of this conference. Laszlo Takacs, CEO, CSO, R&D, Biosystems International Kft. Hungary, stated that epitope complexity is the result of genetic code, and is dependent and independent on proteome variability, which can change with disease states. Currently, proteome/epitome biology is an unexplored source of biomarkers. In order to investigate this Laszlo Takacs presented an epitope specific non-redundant monoclonal antibody (mAb) library that ran on suitable turnkey antibody biochip platform- The Randox Evidence Investigator. An example, using QuantiPlasm69 Kit, which identified 3 mAbs that could discriminate between lung cancer patients and healthy individuals (unpublished results). It was proposed that the combination of these three markers with classical markers may potentially increase their discriminative power.

Austin Speier, Director, Emerging Technologies, Precision Bioservices, discussed new diagnostics in the U.S. and how that landscape is changing in terms of FDA regulation. There are two pathways required to get a new diagnostic tool into the market, i.e., make it a kit or to form a lab partnership. In addition, new approaches by the FDA to regulate lab development were discussed. This consists of both *The Framework Guidance* (in where the FDA provides a risk-based approach to FDA oversight and implementation schedule) and *The Notification Guidance* (which is a new regulatory paradigm to replace formal registration and listing requirements).

Mike Taussig, Head of the Protein Technology Group, The Babraham Institute, stated that protein microarrays can allow parallel miniaturized screening of binding events of large numbers of proteins of up to 20,000 human proteins. This technology is being increasingly applied for:

1) Antibody specificity and cross-reactivity screening
2) Detection of auto antibodies in serum or other fluids and auto antigen discovery
3) Protein-protein interactions
4) Targeting of post-translational modifications
5) Drug target discovery and off-target reactivity

A protein microarray, also referred to as a protein chip, is a high-throughput method used to trace the activities and interaction of proteins (Melton 2004). Furthermore, the method can determine protein function both on a small and large scale. This provides a research advantage in that a large number of proteins can be tracked in tandem.

Mike Taussig and group have demonstrated that the DAPA method (DNA Array to Protein Array) can provide a cost effective and convenient way of producing protein arrays on demand and that DAPA is expected to facilitate the application of personalized medicine and screening purposes (Schmidt et al. 2013). In addition, in a different study, Mike Taussig and group reviewed the requirements for a pipeline production of protein binders for the human proteome (Taussig et al. 2013). This included:

1) Target prioritization
2) Antigen design
3) Next generation methods
4) Data bases and approaches that were taken by ongoing projects in Europe and the USA

It was suggested that since there are tremendous technical, personnel, and financial resources needed to accomplish these goals the efforts might be more effectively addressed by large-scale international collaboration.

Anton Ussi discussed EATRIS ERIC- the European Infrastructure for Translational Medicine. The discipline of translational medicine projects the goal to ameliorate the health of both the individual and community by explaining or "translating" the findings from diagnostic tools, medicines, procedures, policies, and education. EATRIS ERIC is a new legal entity that is directly pertinent across the European Union. It is also a permanent, independent, and non-commercial infrastructure with long-term commitments from member governments: Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden, the Netherlands, and the United Kingdom. The main mission of EATRIS ERIC is to support researchers in developing their biomedical discoveries for novel preventative, diagnostic, or therapeutic products up to clinical proof of concept; and to develop a healthy pipeline.

Heinrich Roder, Chief Technology Officer, Biodesix, discussed deep learning and molecular diagnosis with matrix-assisted laser desorption ionization (MALDI) which is a highly reproducible sophisticated spectral processing. He stated that the benefit of deep MALDI compared to the standard MALDI techniques is that they allow for a higher degree of sensitivity by measuring the expression of hundreds to thousands of serum proteins. Deep learning incorporates machine learning algorithms (inspired by brains) that are based on learning multiple levels of abstraction/representation, which can be seen as meta-learning.

Heinrich Roder provided several examples of predictive test for an immunotherapy (GI-4000) on adjuvant treatment of pancreatic and breast cancer prognosis from mRNA data. In terms of the current state of this technology, multiple classifier problems were solved, a unique feature set has been obtained, and the combination of mini-classifiers with dropout (CMC/D) generalize well at convergence.

The General Session

The final portion of this conference featured five 10-minute oral presentations from exemplary submitted abstracts.

Dana Jurkovicova, KRD Molecular Technologies, discussed the clinical utility of miRNA biomarkers in patients carrying the BRCA1 mutation. It was demonstrated that miRNAs- miR-155, miR-21, miR-27a, and miR-17~92 oncogenic clusters are appropriate candidates for breast cancer diagnostic/prognostic, in addition to being potential therapeutic points. In this way, the profiling of certain miRNA biomarkers from peripheral blood signifies a non-invasive platform for breast cancer diagnosis, staging, and therapy monitoring.

Christopher Walton, Lecturer in Analytical Technology, Institute for Environment, Health, Risk, and Futures, Cranfield University, discussed the use of *para*-cresol (4-methylphenol), which is a volatile organic compound, as a biomarker and interest for point-of-care application for *Clostridium difficile* infection. This has potential in diagnostics as *para*-cresol is produced by Clostridium and not by any other species, and it is a possible compound measure of both bacterial activity and virulence.

Gary Sweeney, Professor, York University, Toronto, Canada; President, Toronto BioScience, discussed adipokines as potential biomarkers for diabetes. Adipokines are hormones secreted by adipose tissue and the amount that is secreted is altered in obesity. For example, adipokine- adiponectin levels are decreased in obesity.

Therefore, some adipokines have potential in the early diagnosis and treatment monitoring of chronic diseases, e.g., obesity, diabetes, and cardiovascular disease.

Philipp Schatz, Head, Biomarker Program, Metanomics Health BmbH, discussed the development of new metabolomics as diagnostic biomarkers. One biomarker that was discussed was CLIA-ready for congestive heart failure diagnosis, which demonstrated good sensitivity and specificity biomarker assay performance in heart failure with reduced ejection fraction.

Robert McCormack, Head of Circulating Tumor Cell R&D, Janssen Oncology Research and Development, Johnson & Johnson, discussed utilizing circulating tumor cells as valid biomarkers, e.g., SWOG S0500 (SABCC 2013). This biomarker was tested in a randomized phase III trial and demonstrated that patients with metastatic breast cancer did not improve from change or alternative chemotherapy in patients whose circulating tumor cell levels did not decrease to <5 cells/7.5ml after a single cycle of first-line chemotherapy.

Concluding Remarks

Overall, this was an excellent conference which clearly demonstrated why biomarkers are becoming an important aspect in medicine for screening, diagnosis, and disease monitoring. As we have seen in this report they can also be genetically stratify and these tests results can assist in selecting initial therapy for likely responders, identify patients with high risk of severe adverse events, identify subgroups at risk for disease progression, and monitor drug therapy success. The concept of liquid biopsies and multimodal testing has become more prevalent as well; as is evident in several of these presentations. Predictive and prognostic benefits of biomarkers may provide utility in evaluating chronic conditions, e.g., rejections after cardiac transplantation, monitoring Huntington disease treatment dose selection, and the ability to monitor response to treatment in multiple myeloma. In addition, we have seen several examples where biomarkers will play a pivotal role in the future of early detection and diagnosis of several cancers, e.g., colon, ovarian, lung, and prostate; as well as in non-cancer conditions like Alzheimer disease. However, we have also seen that biomarkers face difficulties in development and being brought to market.

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