White Paper

Developments for a growing Japanese patient population: Facilitating new technologies for future health care

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Lung cancer, COPD and cardiovascular diseases are highlighted as some of the most common disease that cause mortality, and for that reason are the most active areas for drug development. This perspective paper overviews the urgent need to develop a health care system for a rapidly growing patient population in Japan, including forthcoming demands on clinical care, expecting outcomes, and economics. There is an increasing requirement to build on the strengths of the current health care system, thereby delivering urgent solutions for the future. There is also a declaration from the Ministry of Health, Labour and Welfare (MHLW), to develop new biomarker diagnostics, which is intended for patient stratification, aiding in diagnostic phenotype selection for responders to drug treatment of Japanese patients.

This perspective was written by the panel in order to introduce novel technologies and diagnostic capabilities with successful implementation. The next generation of personalized drugs for targeted and stratified patient treatment will soon be available in major disease areas such as, lifestyle-related cancers, especially lung cancers with the highest mortality including a predisposing disorder chronic obstructive pulmonary disease, cardiovascular disease, and other diseases. Mass spectrometric technologies can provide the “phenotypic fingerprint” required for the concept of Personalized Medicine. Mass spectrometry-driven target biomarker diagnoses in combination with high resolution computed tomography can provide a critical pathway initiative facilitated by a fully integrated e-Health infrastructure system.

We strongly recommend integrating validated biomarkers based on clinical proteomics, medical imaging with clinical care supported by e-Health model to support personalized treatment paradigms to reduce mortality and healthcare costs of chronic and co-morbid diseases in the elderly population of Japan.

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The future medical treatment of patients is expected to have an increased need to combine diagnosis such as imaging and biomarkers with selection of drug prescriptions for patients. These expected developments are currently being assessed by the FDA and NIH, in collaborative programs and studies with the Pharma industry.

To address the future challenges that Japanese society is facing, novel technologies and diagnostic capabilities must be developed and implemented throughout the coming decade. It is steadily advancing to discover novel target biomarkers that are directly related to pathophysiology and etiology, and to develop diagnostic strategies with those markers. Imaging modalities including high resolution computer tomography (HRCT), magnetic resonance imaging (MRI) and positron emission tomography (PET) have been commonly used for diagnosis in average Japanese hospitals and even in healthcare clinics. However, these proteomic and imaging methods are now being used separately and provide mutually independent information. COPD involves multiple compartments in the lung, such as the Airways, parenchyma, as well as to lung cancers. Japan is the world’s largest market for tobacco products (smoking rate at 29%) and has COPD prevalence estimates similar to western countries with over 5 million COPD patients [1]. The cost impacts of COPD in Japan have been huge and estimated at 805.5 billion ¥ (6.8 billion US$) per year; 645.1 billion ¥ (5.5 billion US$) in direct costs and 160.4 billion ¥ (1.4 billion US$) in indirect costs (direct and indirect costs are split as 80% to 20%). COPD is a preventable disease with cessation of smoking, which has widely been promoted to reduce the prevalence of the disease; it will take longer time for the promotion to become indeed effective. Given its complexity and the long term effects of smoking, COPD requires early detection and therapeutic evaluation with comprehensive multi-modalities, and further detection and management of co-morbidities (such as lung cancer and heart disease) that modify outcomes of the primary disease [2,3]. Lung cancer is a “multifactorial” disease, i.e., many factors work together to cause the disease. Most lung cancer patients actually have COPD with progressed emphysema and infectious disease agents such as Chlamydia pneumoniae, human papilloma virus (HPV) and measles [4–6]. Possibly, these factors in combination with certain genetic changes may be the initial cause of lung cancer. Researchers are now beginning to isolate some of the genomic factors that are associated with an increased risk of lung cancer. Paradoxically, the incidences of chronic heart disease (CHD) and atherosclerosis in Japan have been in decline. This may be attributed to lower serum cholesterol, declining rates of smoking and declining trends in blood pressure [7]. However, CHD continues to be a major cause of death in smokers with different co-morbidities. A number of studies in Japan have shown that smoking increases the risk of premature death among both men and women. In conclusion, it is likely that environmental factors, in addition to organic cooking (mostly in Asian countries), as well as occupational reasons in addition to smoking are risk factors that contribute to the development of cancer and CHD. Thus, the smoking effects are the major factors for these diseases.

Currently there are 109 unique protein biomarkers used daily in the clinic [8,9]. There are limited studies available for biomarker of diseases except some of the cancer biomarkers until today. Examples like; human epidermal growth factor receptor 2 (HER2), KL6, SA100, prostate specific antigen (PSA) and creatine phosphokinase (CPK) are some markers that are used globally today.

Within lung cancer, there have been reports on early indication of somatic mutation appearances within the EGFR receptor. The increased mutation frequency was observed especially in Japan and Asia [10]. The Japanese lung cancer patients showed to have a certain percentage of non-responders, the reason for this was not well understood at the time. At a later time point, when the number of Gefitinib (IRESSA) treated patients increased to tens of thousands, the mutations within the EGFR-receptor was discovered at high frequencies [8,11–13]. Later, these somatic mutations were shown to have a direct link to the specific inhibitory effects of IRESSA. Today, an EGFR-mutation assay outcome will guide the clinicians in Japan, to what treatment and medication to use for these patients. Epidermal growth factor receptor is associated to resistance to chemotherapy as has been the case with radiation therapy. The restricted treatment efficacy opened up for novel drugs such as Gefitinib and Erlotinib, developed as specific EGFR-tyrosine kinase inhibitors (TKI), with good efficacy and less side effects. A recent study also presented the situation in Europe [14].

It is evident in Asian populations that the majority of the non-small cell lung cancer (NSCLC) patients with activated mutations achieved a durable and effective response to EGFR TKI-treatment, such as Gefitinib [15,16].

The somatic mutation assay test has now been put into place in Japan, and is used routinely to identify the various lung cancer phenotypes. In addition, a large case-control study was conducted in Japan, involving 52 clinical centers throughout Japan. This epidemiological study was also directed towards biomarker discovery and probably makes it the biggest clinical Biomarker Discovery study undertaken within the industry [17,18].
vessels, and causes remodelling and destruction, which can vary among individuals. The genetic basis for such a difference in susceptibility and disease presentation is currently being elucidated and potential genes implicated are currently validated [19]. CT offers a non-invasive approach to image COPD disease changes [20] at a spatial resolution of 0.5 mm in X and Y directions and 1 mm in Z direction which helps in accurately resolving changes in airways of around 2 mm [21]. However, additional novel techniques like optical coherence tomography (OCT) can provide a spatial resolution of around 3 to 16 μm and an ability to image at a surface depth of 3 mm [22]. Currently, new developments are progressing where the combination of HRCT imaging and target biomarker expression analysis may assess a correlation between histopathological changes and biomarker levels. This interdisciplinary approach will help to identify disease at an early stage and the degree of progression, and thus to improve an individual patient’s outcome. Upon drug treatment, changes in the CT-image and biomarker assay read-outs will indicate outcomes for the patient. The ultimate goal would be to monitor the treatment response in clinical and functional variables that show good correlation to CT measurements with HRCT, with less variability than the placebo group.

Another important consideration, which remains as a top priority for future Personalized Medicine developments, is the drugs with low frequency of adverse events. Patient safety, which relates to the minimization of side effects, is crucial in order to limit the suffering of patients, as an effect of drug use.

Japan has declared a pricing strategy that includes request for new biomarker diagnostics that can be used for patient stratification, with phenotype selection for responders to drug treatment [23]. In this declaration, pharmaco-genomic, and proteomic technologies are promoted in the discovery and development of drug related biomarkers by the drug pricing committee within the Ministry of Health, Labour and Welfare (MHLW), (http://www.mhlw.go.jp/shingi/2009/07/dl/s0715-9a.pdf).

The pricing strategy will be used in order to promote safe and efficient approved drugs for the treatment of Japanese patients.

2. Protein biomarker diagnosis

Detection of new biomarkers of emphysema and inflammatory reaction in the lung and heart can aid in early identification of disease and in monitoring the effect of therapeutic agents on disease progression. There is currently much research activity in this area but no consensus regarding which bio-molecules are most useful for the identification of COPD progression or for predicting clinical outcomes.

It is expected that multiplexed biomarker assay platforms will play an important clinical role as becoming a complement to traditional immuno-assays for future molecular diagnostics. An early evidence of the progress developments is that recently, the interagency group of the National Cancer Institute and the Food and Drug Administration (NCI-FDA) presented the validation of protein based multiplex assay [24]. In addition, they reported on Multiplexed Biomarker Assay Platform developments where the NCI-FDA Oncology Task Force, members of the Clinical Proteomic Technology Assessment for Cancer program, are evaluating both antibody based multiplexing as well as mass spectrometry based MRM assays [25].

Multiplexed biomarker assay platforms are expected to be the key platforms that will help improve the clinical health care, and targeted medication in the future. The mass spectrometry based MRM assay panels would be using the same SRM/MRM principles as for drug and metabolite monitoring. These quantitative multiple reaction monitoring (MRM) methods have been in use for more than a decade in the development of new medicines, and this has been in close collaboration with the FDA.

Currently the available triple-quadrupole mass spectrometers have both improves sensitivity, mass accuracy as well as scan speed that is in line with the multiplex measurement principle.

3. Multiplexed biomarker assay platforms

Mass spectrometry-based selective reaction monitoring is rapidly developing with an expectation to become a preferred technology for the development of quantitative protein or peptide assays with high sensitivity and selectivity for clinical research [26,27]. Its sequential application to multiple targets at once MRM delivers high-throughput, and when taken together, these parameters provide a breakthrough quantification methodology. This technology allows absolute biomarker quantification in very small amounts of bio-fluid samples, allowing multiplexed read-outs of disease panels.

Assay formats with multiple hundreds of proteins/assay have recently been presented [28,29]. It is expected that clinical assay panels with 100 proteins/assay, screening both blood samples and tissues will be standard in laboratories around the world in the near future. The MRM assay format measures specific target proteins by monitoring proteotypic (unique to the target protein) peptide sequences. The technology is fully quantitative when isotopically labeled internal standards are included in the assay. No immuno-reagents are required for MRM assays in principle but immuno-precipitation or other affinity enrichment techniques may be used in sample preparation to enhance the sensitivity of the assay. The MRM technology is performed on triple quadrupole mass spectrometers and provides precise quantification and broad dynamic range, even within highly complex sample matrices. The multiplex MRM assays allow high density data generation in clinical diagnosis, where it is envisioned that multiple MRM-panels can be run simultaneously. This would provide a whole new setting, whereby the health care system would perform future patient diagnosis. In fact, immunoassay platforms like ELISA, with extensive robotics and automation would face major difficulties fulfilling these performances. Even with current synthesis technologies of isotope labeled internal standards, it makes MRM-assay costs highly competitive in comparison to current pricing in the clinical hospitals running clinical assays.

In addition, when mass spectrometry is coupled with a front-end sample introduction system such as nano-flow liquid chromatography, the limit of quantification/detection of target peptides/proteins and biomarkers may reach low
attomole levels. The utilization of this technology makes analysis of clinical “fingerprint” target biomarkers in common body fluids not only possible, but also an attainable goal for the future. Recent promising efforts to combine MRM with sampling at histological levels [30], will facilitate finding the body fluid targets of which levels correlate with those at disease foci, serving as a diagnostic strategy combined with HRCT. MRM delivers a unique signal that can be detected and quantified in the midst of a very complicated biological matrix. The mass spectrometry spectra plots are simple, usually containing only a single peak for each MRM. This characteristic makes the assay especially suitable for sensitive and specific quantitation [31].

The latest developments within the MRM technology are providing high density assay panels with high sensitivities, allowing low abundant level proteins to be quantified, even down to copy numbers as low as 40 copies/cell [28].

In comparison with ELISA immunoassays, recently MRM panels were presented in blood plasma with linear operational performance down to low pg/ml [24].

Imaging using CT, MRI, ultrasound, molecular imaging is commonly used in clinical practice and also in therapeutic trails. They help in non-invasively quantifying regional disease, which is critical for validating clinical proteomic biomarkers elucidated from different tissue compartments.

Computed tomography (CT) is considered a novel modality to estimate the key pathological changes in COPD patients, namely emphysema and airway remodeling. Japan is in the forefront of CT technology and has access to the advanced scanner hardware and required expertise in radiology and informatics. CT offers a non-invasive approach to image COPD disease changes [20] at a spatial resolution of 0.5 mm in X and Y directions and 1 mm in the Z direction which helps in accurately resolving changes in airways of around 2 mm [21]. By accurate quantification of the disease pathology CT allows phenotyping (or patient stratification) for evaluating novel treatments or determining prognoses. Several academic groups and large chest radiology consortia like the Fleischner Society (www.fleischner.org/) continue to bring novel insights into the application of CT technology and standardization of the method for evaluating COPD and the Big3 diseases, i.e., “lung cancer”, “COPD” and “atherosclerosis”. By using automated CAD tools in batch mode, image analysis and quantification can be done in high-throughput allowing application to large-scale databases.

However, in addition novel techniques like optical coherence tomography (OCT) can provide a spatial resolution of around 3 to 16 μm and an ability to image at a surface depth of 3 mm [22]. MRI imaging using hyperpolarized gases like helium, xenon and fluoride and molecular imaging with PET offer exciting insights into functional status.

Lung cancer imaging using CT together with PET for imaging the volume and functional status of lung nodules is widely used in clinical setting. These tools are used in screening of large cohorts of smokers and currently the benefits of screening are being evaluated. Together with tumor based proteomic biomarkers, imaging offers strong model to related function, structure and disease stage with proteomic fingerprint print, thereby supporting the validation of clinical proteomic endpoints in smoking related lung diseases. In addition, a large part of the lung cancer patients with diagnosed tumors, also show radiological evidence of emphysema and airway disease [32,33].

Critical path initiative (CPI) is the US national strategy for transforming the way FDA-regulated products are developed, evaluated, manufactured, and used with a focus on accelerating the development of safe and efficacious novel treatments (http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm). CPI has initiated several opportunities centered around the development and validation of novel biomarkers for smoking-related diseases including soluble biomarkers, patient-reported outcomes and imaging. NHLBI/NIH has initiated a program for Sub Populations and InteRmediate Outcome Measures In COPD (SPIROMICS), which focuses on combining biomarkers and imaging endpoints for outcome assessment in COPD patients.

In eHealth developments, the exchange of health information electronically between physicians, hospitals, health plans, and patients has increased substantially in the last year and is reducing the cost of care and positively impacting physicians, according to a new survey released by the non-profit eHealth Initiative (eHI) today. “Migrating Toward Meaningful Use: The State of Health Information Exchange,” a report based on eHI’s Sixth Annual Survey of Health Information Exchange, presents a very clear benefit to the health care system. Responses from operational initiatives demonstrate an increasingly positive impact on the efficiency of care while showing a return on investment.

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REFERENCES


