What are the Prospects for -Oomics- Based Molecular Technologies in Cancer Diagnostics and Treatment

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WHAT ARE THE PROSPECTS FOR -OMICS-BASED MOLECULAR TECHNOLOGIES IN CANCER DIAGNOSTICS AND TREATMENT?

by

Katya Eriksen

AN UNDERGRADUATE THESIS

Presented to the Faculty of
The Environmental Studies Program at the University of Nebraska-Lincoln
In Partial Fulfillment of Requirements
For the Degree of Bachelor of Science

Major: Environmental Studies
With the Emphasis of: Environmental Studies Public Health

Under the supervision of:

Thesis Advisor: Dr. Chandran Achutan (UNMC, College of Public Health)

Thesis Reader: Dr. Christine Haney Douglass (UNL, IANR)

499A Course Instructor: Dr. David Gosselin (UNL, IANR)

Lincoln, Nebraska

April, 2019
ABSTRACT
WHAT ARE THE PROSPECTS FOR -OMICS-BASED MOLECULAR TECHNOLOGIES IN CANCER DIAGNOSTICS AND TREATMENT?

by

Katya Eriksen, B.S.

University of Nebraska, 2019

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ABSTRACT:

Cancer remains one of the leading causes of death in the United States, following the heart disease. New technologies are needed to fight and eventually to eradicate cancer. Omic technologies is a new emerging field of cancer research that may offer cancer patients long awaited opportunities to get faster, more precise personalized medical care, while letting doctors do their job more effectively. The rapid development of omic technologies and large datasets promise a new type of health care system when the patients can be treated according to their own individualized molecular characteristics.
PREFACE (ACKNOWLEDGEMENTS)

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Thesis Reader: Dr. Christine Haney Douglass (UNL, IANR)

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INTRODUCTION

Cancer remains one of the leading causes of death in the United States, following the heart disease. No one is immune to developing cancer: kids and adults, men and women. The risk of developing cancer usually increases with age, carcinogenic exposures, poor nutrition, inactive life style, excessive sun exposure, infectious agents and genetic predisposition. With cancer mortality rates declining due to the anti-smoking educational campaigns, immunizations and cancer screenings, the demand for cancer treatments remains high. That is why cancer detection and diagnosis must be early and accurate. Patients with cancer face an ever-widening gap between the exponential rate at which technology improves and the linear rate at which these advances are translated into clinical practice (Blau et al., 2012).

New technologies are needed to fight and eventually to eradicate cancer. Omic technologies is a new emerging field of cancer research that may offer cancer patients long awaited opportunities to get faster, more precise personalized medical care, while letting doctors do their job more effectively.

Omic technologies are primarily aimed at the universal detection of genes (genomics), mRNA (transcriptomics), proteins (proteomics) and metabolites (metabolomics) in a specific biological sample (Horgan et al., 2011).

Omic technologies are providing remarkable opportunities for a better understanding of exposure and prediction of potential adverse health effects. Omic technologies are increasingly important for the understanding of cancer molecular mechanisms.
“Cancer genomics” refers to the study of tumor genomes using various profiling strategies including (but not limited to) DNA copy number, DNA methylation, and transcriptome and whole-genome sequencing—technologies that may collectively be defined as omics. The goal of cancer genomics is to survey these omics data to identify genes and pathways deregulated in cancer and reveal those that may be useful for the detection and management of disease. Such discoveries will improve our understanding of the biology of cancer and lead to the discovery of novel diagnostic, prognostic, and therapeutic markers that will ultimately improve patient outcomes. The field of cancer genomics is rapidly evolving and coupled with the ever-increasing efficiency of genomic profiling; this has led to the realization that personalized medicine is likely to soon become a reality. It is hopeful that in the near future, tumors of cancer patients will be profiled in a timely manner and that the tumor omics findings will subsequently be used to inform patient management (Vucic et al., 2012).

Recent studies (Conrad et al., 2007, Chen et al., 2012, FDA-NIH Biomarker Working Group, 2016) indicate that microarray based genomic and mass spectrometry based proteomic technologies are powerful tools for classification of tumor sub-types. In addition, these techniques can be used for the identification of genes or proteins that may serve as diagnostic, predictive, or prognostic markers. Omic technologies’ use for cancer staging and personalization of therapy at the time of diagnosis could improve patient care (Goney et al., 2017).

Today’s conventional symptoms-oriented disease diagnosis and treatment has a number of significant limitations: for example, it focuses on only late/terminal symptoms and generally neglects preclinical pathophenotypes or risk factors. It generally disregards the underlying mechanisms of the symptoms. The disease descriptions are often quite broad so that they may actually include multiple diseases with shared symptoms. The reductionist approach to identify
therapeutic targets in traditional medicine may over-simplify the complex nature of most diseases. Advances in the ability to perform large-scale genetic and molecular profiling are expected overcome these limitations by addressing individualized differences in diagnosis and treatment in unprecedented detail (Chen et al., 2012).

The rapid development of high-throughput technologies and computational frameworks enables the examination of biological systems in unprecedented detail. Patients can be treated according to their own molecular characteristics. Individual omes as well as the integrated profiles of multiple omes, such as the genome, the epigenome, the transcriptome, the proteome, the metabolome, the antibodyome, and other omics information are expected to be valuable for health monitoring, preventative measures, and precision medicine. Moreover, omics technologies have the potential to transform medicine from traditional symptom-oriented diagnosis and treatment of diseases towards disease prevention and early diagnostics. Personalized or precision medicine is expected to become the paradigm of future health care, owing to the substantial improvement of high-throughput technologies and systems approaches in the past two decades. I would like to do a research on the prospects for omic technologies in our health system, advantages and disadvantages of omic technologies in diagnosis and treatment of cancer (Chen et al., 2012).

Materials and Methods

I have conducted systematic literature review of the recent decade’s medical peer-reviewed publications and peer-reviewed medical research studies. For my research I have used PubMed, PubMed Central, National Center for Biotechnology Information databases and government publications about the use of Omic technologies in cancer diagnosis and treatment. I have used the following terms when searching for articles: omic technologies, cancer,
biomarkers, genomics, cancer genomics, epigenomics, transcriptomics, proteomics, metabolomics.

I have examined collected published articles related to omic technologies and cancer diagnosis and treatment. I have identified promises and limitations of Omic technologies in cancer diagnosis and treatment and the prospects for Omic technologies in cancer diagnostic and treatment in personalized precision medicine of the future based on these published articles.

I have used a specific inclusion criteria for the selection of the articles to use in my research:

Articles must be directly related to my project;

Articles must be Peer reviewed;

Articles must be less than twelve years old;

Qualitative and quantitative studies to be included;

Articles must be based on US studies as well as international studies.

Results

Omic technologies certainly have the potential to transform our health care system from traditional system-oriented to personalized, precision-oriented health care system, that would allow cancer patients to be treated according to their own individual molecular structures.

Omic technologies are beneficial to cancer research. The DNA from many types of cancer have been sequenced, including breast cancer, chronic lymphocytic leukemia,
hepatocellular carcinoma, pediatric glioblastoma, melanoma, ovarian cancer, small-cell lung cancer, and Sonic-Hedgehog medulloblastoma, and databases are established, such as the Cancer Cell Line Encyclopedia (Chen et al., 2012).

Omic technologies would offer a look into each cancer patient’s susceptibility to disease, using preventive medicine and cancer monitoring from the early stages of its development.

Unfortunately, Omic technologies are not the only factors in cancer diagnostic and treatment. Patient’s environment, nutrition, levels of sleep, stress and exercise would have to be added for consideration to the genome structure data for a complete picture of cancer disease development and treatment.

There are many other concerns and questions exist about Omic technologies and its use in personalized medicine. High costs, lack of one standardized methods, technologies and regulatory practices, workforce training, security measures in regard to personal genome data.

Planning, processes standardization, elimination of systems deficiencies and biases, implementation will take time and a collective effort of scientists, doctors, patients, government agencies, computer technologists, etc.

Discussion

The technological advances in the use of Omic technologies in cancer research promise hope to many cancer patients. Technologies that can accurately detect cancer in its early stages will help us to minimize cancer deaths rates and have more successful cancer treatments outcomes.
There are many challenges related to the development of a system that would be able to predict health risks of an individual patient, give an individualized diagnosis, and determine the right treatment and disease management processes.

Current technological advancements in Omic technologies allow scientists to collect and analyze large genome data sets, translating them into useful data in cancer diagnosis and treatment. Many barriers still exist before these new technological advances can form precision public health model for the benefit of any individual cancer patient or a population.
Omic Technologies and Biomarkers

Omic technologies refer to a group of sciences that have foundations in biology. Omic technologies focus on completing comprehensive assessments of molecules in biological systems. The assessments identify biological differences in pathways and processes between a diseased and a non-diseased condition. By identifying the specific pathway leading to a disease, researchers are able to find the conditions that make an individual have a predisposition to either a) develop the disease condition or b) have a protective or favorable effect that prevents a disease (Hasin et al., 2017). For example, an individual with the BRCA 1 and 2 gene mutations is more susceptible to developing breast cancer than an individual who does not have the BRCA 1 and 2 gene mutations (FDA-NIH Biomarker Working Group, 2016).

While many variations of “omic” exist, they are placed into one of six recognized categories of “omics”:

Genomics – Used to identify genetic variants associated with diseases in the human population

Epigenomics – Used to identify genetic changes to DNA and RNA that regulate gene transcription

Transcriptomics – Used to identify RNA transcription variations that produce proteins for cellular structures and cellular regulation

Proteomics – Used to identify protein interactions within a cell

Metabolomics – Identifies cellular metabolic function by its products and by-products

Microbiomics – Used in identifying the microbiota community of bacteria, virus, and fungi that interact with humans.
By using multiple types and variants of Omic technologies the causative pathway or process that leads an individual from a normal condition, pre-disease, to a diseased condition can be identified. The causative pathway or process that defines if an individual has an increased susceptibility or protection from a disease condition is identified as a biomarker (FDA-NIH Biomarker Working Group, 2016).

Omens technologies use a tool called “Integrative Clustering of Multiple Genomic Data Types (iCluster)” This tool is a tool that allows integration of independent sets of clusters or groups of genes in which expression changes are observed under a certain condition (McHale CM et. al., 2013)

Fig. 1
Integration of heterogeneous data sets is based on the recognition of interactions between cellular components merging information across OMICS. Epigenome and microRNAs influences gene expression and protein expression, leading to changes in metabolism (McHale CM et. al., 2013).

Transcriptomics are also used in Environmental Cancer Risk Assessment by comparing a particular sample to a large number of mRNA transcripts. Our genes change in response to environmental exposures. Therefore, gene expression profiling is used to identify genes or transcripts that show different expression as a response to different environmental fluctuations,
time points or cell types. In molecular epidemiology studies transcriptome data can be used to compare gene expression profiles between subpopulations, for instance between a group of individuals with similar characteristics, such as a specific exposure or disease, and a reference group. This reference group usually consists of healthy individuals or unexposed individuals that are matched by age and sex.

Other relevant characteristics, such as smoking status or exposure to other environmental exposures should also be matched or adjusted for in the analyses. Based on the genes that are differentially expressed in these groups, characteristic gene profiles, often derived from blood samples, are identified as potential biomarkers (McHale CM et. al., 2013).

Over the last 10 years the number of publications in environmental cancer research, applying high-throughput OMICS technologies, has increased gradually:

![Graph showing the increase in publications](image)

**Fig. 2**
In the last 10 years the number of publications related to epidemiological cancer research has been increased drastically. The numbers are based on a pubmed search including the following search term: (((((high-throughput sequencing) OR next-generation sequencing) OR RNA-sequencing) OR microarray) OR transcriptome) OR transcriptomics') AND (((((epidemiology) OR epidemiologic) OR population-based) OR case–control study) OR cohort study) OR cross-sectional study) AND cancer AND human (McHale CM et. al., 2013).
A biomarker is defined by the FDA and NIH as "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives" (FDA-NIH Biomarker Working Group, 2016). To be used for diagnostics or drug development, an ideal biomarker needs to be highly specific and sensitive (Halim A, 2011).

Biomarkers can be used in the detection of diseases (diagnostic biomarkers), determining the risk of developing the disease (susceptibility biomarkers), determining if a disease will be aggressive in developing (prognostic biomarker), substituting clinical outcomes (surrogate biomarkers), and toxicological response mechanisms (predictive biomarkers) (European Commission, 2013).

In bio monitoring, biomarkers can be used to accurately and repeatably measure and determine an individual’s exposure to a substance. For example, lead levels in blood, the biomarker is the range of lead levels found in blood that correspond to the development of a disease and necessary treatment. For exposure assessments, predictive biomarkers are useful in understanding a dose-response relationship to an exposure (Everson et al., 2018).

Another example of the use and understanding emerging from Microbiomics is well described by the Rajppoot research team: it has been shown that the microbiota of healthy versus diseased individuals is distinct. An altered microbiome (a microbiome from a disease individual) has been linked to an over expression of specific genes linked to cancer. As a result, the screening of microbiota my result in early detection of a disease. The biomarker in this case
would be the microbiome associated with a disease or non-diseased individual (Rajpoot et al., 2018).

Overall, using “omics” to build an understanding of how the individual systems function and respond to an exposure allows a researcher, investigator, or clinician to use a biomarker to determine the extent of the exposure and the increase in risk associated in the development of a disease condition and to use effective treatments. However, it is important to note that omics and biomarkers are designed for populations as a whole and not for an individual, as there is a range of susceptibility with having or lacking a biomarker. To illustrate this, having the BRACA 1 or 2 gene mutations does not guarantee an individual will develop breast cancer; having the gene mutation, instead increases the likelihood of developing the disease (FDA-NIH Biomarker Working, 2016).

**Omic Technologies: Benefits and Limitations**

Omic technologies is a rapidly expanding field of science that presents great opportunities for humans to better understand environmental exposure and predicts various potential adverse health effects.

The European Commission’s working document/report (2013) analyzes a personalized medicine health care model that could potentially integrate large-scale molecular data with clinical data. This rapidly developing science-driven approach to health care has potentially very great benefits for patients, clinicians and health care systems. The personalized medicine approach can employ a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition
to disease and/or to deliver timely and targeted prevention. Some potential advantages offered by this new approach include ability to make more informed medical decisions, higher probability of desired outcomes thanks to better-targeted therapies, reduced probability of adverse reactions to medicines, focus on prevention and prediction of disease rather than reaction to it, earlier disease intervention than has been possible in the past, improved health care cost containment (European Commission, 2013).

Large amounts of acquired data raise complex challenges for healthcare stakeholders, including patients. These challenges include the following: (i) sample collection, handling, storage, and transport; (ii) data analyses using multi-omics integration techniques; and (iii) collecting electronic medical record data. The integration of medical record data with biological data and their analysis are other issues. Finally, data sharing within the scientific community raises controversial legal, ethical, and privacy concerns as well (Tebani A., 2016).

Other Omic technologies issues and limitations include high cost, reproducibility, ethical responsibility, and retrieval (Biomarkers are derived from body fluids such as blood and urine or even riskier specimens such as human tissue (biopsies) and cerebrospinal fluid). Collection of such specimens are more costly and more difficult to collect (NeuroRx, 2004). Experimental and Analytical Noise (multiple technical platforms produced by different manufactures produce different results) is another challenge associated with Omic technologies. Using standard quality control (QC) processes and metrics to normalize intra-laboratory and inter-laboratory omics measurement variations and applying consistent statistical correction methods and appropriate computational tools can address some technical variation issues (Tebani et al., 2016). Analytical accuracy and clinical relevance, as well as biological variations in patients are current limitations of Omic technologies (Tebani et al., 2016).
With the constant new developments in omic technologies, protecting personal genetic data and privacy becomes a top priority.

Balanced informed consent outlining both benefits and risks are key ingredients for maintaining long-lasting credibility in genetic research. With the active engagements of a wide range of stakeholders from the broad genetics’ community and the general public, we as a society can facilitate the development of social and ethical norms, legal frameworks, and educational programs to reduce the chance of misuse of genetic data regardless of the ability to identify datasets (Erlich et al., 2014).

**Omic Technologies: Future Prospects for Personalized Precision Medicine**

Within clinical research, oncology is expected to have the largest gains from biomarkers over the next five to ten years. Development of personalized medicine for cancer is closely linked to biomarkers, which may serve as the basis for diagnosis, drug discovery and monitoring of diseases. A major challenge in development of cancer biomarkers will be the integration of proteomics with genomics and metabolomics data and their functional interpretation in conjunction with clinical data and epidemiology (Jain KK, 2007).

Network-based methods will effectively facilitate the development and improvement of precision medicine by directing therapies based on the underlying biology of a given patient’s disease. The goal of precision medicine is to identify novel therapeutic strategies that can be optimized for each disease type or each patient based on the underlying genetic, environmental, and lifestyle factors. Pharmaco-omics analyses based on an integration of pharmacology and
various “omics” data types can be employed to develop effective treatment strategies using particular drugs and doses that are tailored to each individual (Turanli et al., 2018)

Current medical practice is being undermined and precision medicine is profoundly reshaping the future of medicine through recent technological advances. Omics technologies are enabling the simultaneous measurement of a huge number of biochemical entities, including genes, genes expressions, proteins, and metabolites. After decades of reductionism, holistic approaches have begun to address inborn errors of metabolism in a systemic fashion. Despite some existing drawbacks, genomics and metabolomics seem to be taking the lead in the race to get into clinical practice. However, challenges such as data quality/integrity, reproducibility, and study sample sizes have to be addressed. According to Tebani research team, the small number of multi-omics datasets and the lack of standardized and harmonized protocols affect the wide dissemination of these approaches. In order to overcome these drawbacks, the Tebani research team suggests that a special attention should be given to validation strategies at all stages. Moreover, the development of new analytical and machine learning methods will facilitate analysis of multi-tissue and multi-organ data, thus enabling a real investigation of systemic effects. Extended and effective resources for biobanking are also essential to ensure consistency. Addressing these challenges will improve healthcare management by moving from a reactive, targeted, and reductionist approach to a more proactive, global, and integrative one (Tebani et al., 2016).

Upgrading laboratory informatics infrastructures and a new medical workforce trained in biomedical big data management are necessary for the successful integration of omics-based strategies. Laboratory workflows with high-quality data acquisition, mining, and visualization are fundamental for fully embracing the four Ps (predictive, personalized, preventive, and
participatory) of precision medicine and effectively translating the underlying biological knowledge into clinically actionable tools (Tebani et al., 2016).

The Precision Medicine Initiative introduced during the Obama Administration is a long-term research endeavor, involving the National Institutes of Health (NIH) and multiple other research centers, which aims to understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease (U.S. National Library of Medicine, 2015).

The Precision Medicine Initiative has both short-term and long-term goals. The short-term goals involve expanding precision medicine in the area of cancer research. Researchers at the National Cancer Institute (NCI) hope to use an increased knowledge of the genetics and biology of cancer to find new, more effective treatments for various forms of this disease. The long-term goals of the Precision Medicine Initiative focus on bringing precision medicine to all areas of health and healthcare on a large scale. To this end, the NIH is planning to launch a study, known as the All of Us Research Program, which involves a group (cohort) of at least 1 million volunteers from around the United States. Participants will provide genetic data, biological samples, and other information about their health. To encourage open data sharing, participants will be able to access their health information, as well as research that uses their data, during the study. Researchers will use these data to study a large range of diseases, with the goals of better predicting disease risk, understanding how diseases occur, and finding improved diagnosis and treatment strategies (U.S. National Library of Medicine, 2015).

The potential for precision medicine to improve health care and speed the development of new treatments has only just begun to be tapped. Translating initial successes to a larger scale will require a coordinated and sustained national effort. Through collaborative public and
private efforts, the Precision Medicine Initiative will leverage advances in genomics, emerging methods for managing and analyzing large data sets while protecting privacy, and health information technology to accelerate biomedical discoveries (The White House, Office of the Press Secretary, 2015).

The steady improvement of high-throughput technologies greatly facilitates this process by enabling omics profiling such as whole genome, epigenome, transcriptome, proteome and metabolome, which convey detailed information of the human body. Integrated profiles of these omes should reflect the physiological status of the host at the time the samples are collected. Personalized omics approach catalyzes precision medicine at two levels: for diseases and biological processes whose mechanisms are still unclear, omics approach will facilitate researches that would greatly advance our understanding; and when the mechanisms are clarified, individualized health care can be provided through health monitoring, preventative medicine, and personalized treatment (Chen et al., 2012).
References


Halim A.-B. Biomarkers in Drug Development: A Useful Tool but Discrepant Results May Have a Major Impact. INTECH Open Access Publisher; Rijeka, Croatia: 2011


# Project Timeline

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# Proposed Budget

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**Total Amount Sought** $85.00 (personal expenses)

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