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Personalized Medicine: The Use of Biomarkers and Molecularly Targeted Therapies for Patient Care and Cancer Intervention

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Personalized Medicine: The Use of Biomarkers and Molecularly Targeted Therapies for Patient Care and Cancer Intervention

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Abstract

Personalized medicine and targeted therapy have been emerging fields of study for the remediation and inhibition of cancer. Personalized medicine in the treatment of cancer involves using genetic, immune, and proteomic profiling to provide therapeutic options as well as prognostic background for every patient and their tumor's genetic mutations. Targeted therapies allow researchers and medical personnel alike to determine the appropriate treatment for a patient based on the molecular basis and mechanistic actions of a cancerous tumor. The overall significance of this study was to express how these treatments use biomarkers to pinpoint the location, and severity of the cancer, and to administer the right treatment. Early detection of tumor-specific biomarkers can allow the use of non-invasive routine monitoring.

The study aims to provide an elaborate explanation on the various biomarker classification and present the protocol on how they are sorted and validated to be a potential cancer biomarker used in clinical practice. Categorizing biomarkers relies on their characteristics. These classifiers will divide them into one of the following groups: general biomarkers, DNA biomarkers, and DNA tumor biomarker. The expressions of microRNA also play a role in the determination of cancer, as most of these clusters regulate the expression and transcriptional activity of various cancer cell lines. The expression of the ER receptors in mammalian cells classifies breast cancer into one of the following categories: triple negative, estrogen receptor (ER) negative, or (ER) positive. ER positive breast cancer patients can positively benefit from personalized medicine as these patients have to undergo specific hormonal therapy and supplementary adjuvant chemotherapy to eliminate the estrogen-induced proliferation of these mammalian cells. Drugs like tamoxifen function as antagonists to the ER receptor to inhibit the transcriptional activity of the ER receptors. Other cancer types such as colorectal cancer, and lung cancer may also benefit from such approaches.

The limitations of the study include the unique genomic profiling of each patient, challenges in validation and implementation of drug combinations, and the deployment of technologies for DNA sequencing.

Keywords: cancer, biomarkers, personalized medicine, gene therapy, targeted therapy, DNA Biomarker, RNA expressions, ER, colorectal cancer, lung cancer, prostate cancer, leukemia, targeted treatment

I. Introduction to Personalized Medicine, Biomarkers, and Targeted Treatment

The release of the first draft of the Human Genome Project (Collins et al., 2002) has allowed scientists and researchers to make much progress in the field of clinical medicine through the discovery of multiple genes. Scientists believe that these genes contribute to the growth and progression of various human illnesses. The Human Genome Project aims to progress the development of personalized medicine, which is an emerging path in the field of healthcare (Collins et al., 2003). Personalized medicine is an evidence-based approach for treating patient health concerns (Chan & Ginsberg, 2011). This approach analyzes the molecular mechanisms involved in the progression and development of the disease to enhance existing health strategies or to develop novel preventive health care measures (Hua et al., 2018). Its goal is to individualize patient care while offering the maximum medical care possible to remediate, and ultimately inhibit, the development of disease. The emergence of personalized medicine has been a promising movement to provide a more effective treatment for progressive diseases. The standard treatments, that are currently available, are quite invasive and limited (Chan & Ginsberg, 2011). Diseases situated in an inaccessible body part, or diseases in more advanced stages, may render treatments, such as chemotherapy, as inadequate to inhibit the proliferation of the disease. "*Typical current*

intervention" dictates treatments and its detection, it is costly to treat with low reversibility probabilities (Chan & Ginsburg, 2011). Novel genome-based drug formulations targeting specific biomarkers are emerging alternatives to general treatments. This formulation can help researchers and clinicians identify the disease and its baseline risks, since diagnostic biomarkers are invariant during disease progression and permit diagnosis in its early stages, thus lowering the cost and risks for the patient (Jain, 2002; Biomarkers Definitions Working Group, 2001).

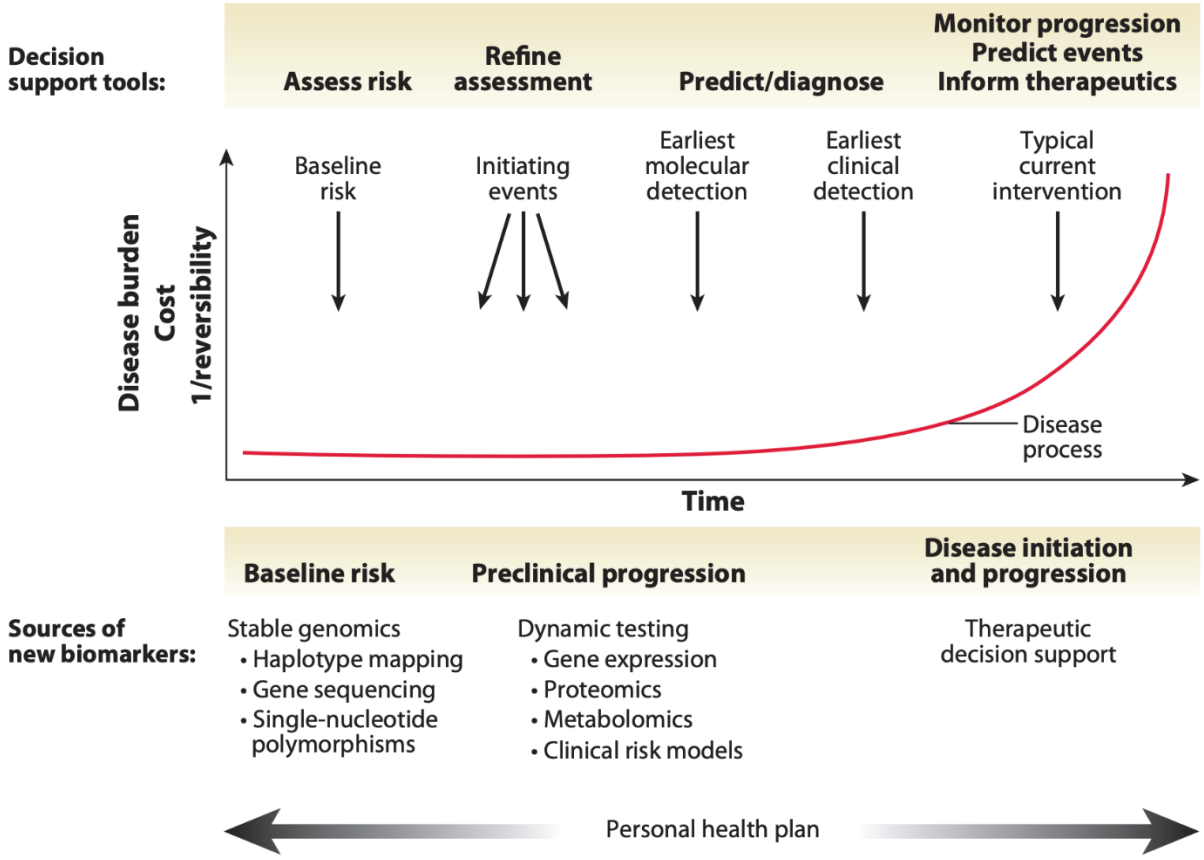

Figure 1. The application of genome-based technologies as personalized health care measures (taken from Chan & Ginsburg, 2011)

The developments in the field of genomics have allowed scientists and researchers to pinpoint specific molecular events which lead to a progressive disease like cancer. These molecular events in the human body are chromosomal rearrangements, gene amplifications, and

other DNA mutations (Leary et al., 2010). These alterations at the genomic level are avoidable by the formulation of novel anti-cancer drugs, and the implementation of tailor-fitted adjuvant therapy to locate the prominent gene expression signatures created by a specific disease. Gene expression signatures can serve as biomarkers, which are biological molecules that function as indicators of body responses (Guo et al., 2016). Biomarkers are biological substances that are measured in the body and may affect the prediction and interpretation of any sickness outcomes (Ganesalingam & Bowser, 2010).

II. Overview of Various Cancer Related Biomarkers

A. Categories of Biomarkers

Biomarkers are useful in personalized medicine by providing better prognostic and predictive markers in comparison to the typical intervention processes (Hamburg & Collins, 2010). This advantage makes it easier for clinicians to provide a better treatment plan for patients. Biomarkers are classified into three distinct classifications: DNA biomarkers, DNA tumor biomarkers, and general biomarkers (Kamel et al., 2017). The discovery of new prognostic and predictive biomarkers drives the paradigm for the exploitation of genomic-based technologies in personalized medicine. Biomarkers are important for monitoring drug responses and deciding which patients will effectively respond to treatments. (Jariyal et al., 2020).

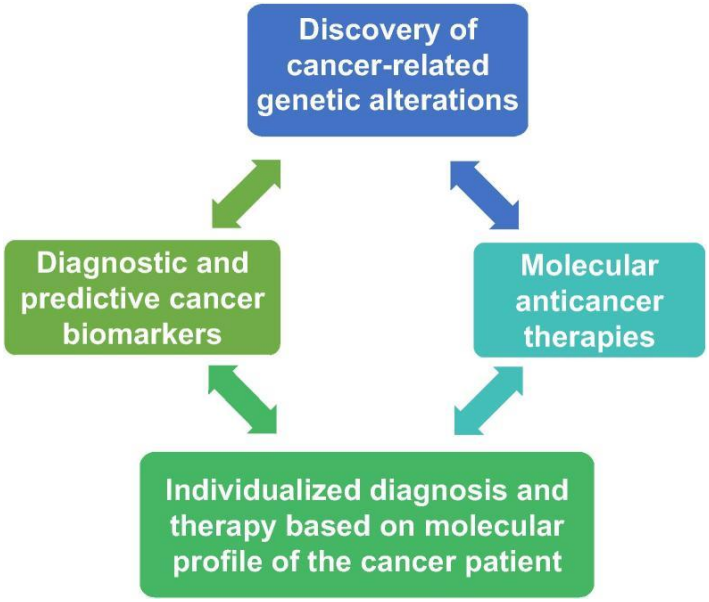

Figure 2. The paradigm for the exploitation of genomic-based technologies in personalized medicine (taken from Kamel et al., 2017).

A.1. DNA Biomarkers

The genetic information coded in the DNA should be stable since the DNA directs the protein synthesis needed for a proper cellular structure and function. DNA biomarkers are small, but distinct, sequence level variations of DNA, which include base pair insertions, deletions, single nucleotide polymorphisms (SNPs) and short tandem repeats (STRs) (Kamel et al., 2017). SNPs are a very common type of DNA biomarker due to the availability of high-throughput sequencing technologies and biological facilities. In addition, SNPs are diallelic in most applications yielding three possible genotypic combinations, which are indicators of epigenetic changes comprised of histone modifications and DNA methylation.

An important consideration about these biomarkers is their stability in comparison with DNA tumor and general biomarkers. Their stability enables the storing of samples for longer periods of time. In addition, DNA biomarkers are reproducible, which deems advantageous in both

prospective and retrospective studies. Furthermore, these biomarkers have simpler storage and handling protocols, which yields a lower cost compared to the other biomarker types. However, DNA biomarkers cannot be of use for therapy monitoring and pharmacodynamics since the alterations made during the initiation of the disease remain the same throughout the advancement and proliferation of the disease (Ganesalingam & Bowser, 2010).

A.2. DNA Tumor Biomarkers

DNA tumor biomarkers, on the other hand, are rearrangement-associated biomarkers specific to a cancerous tumor. Such alterations are present in the early stages of tumor formation and continue throughout tumor development. These tumor-specific chromosomal alterations can be specific biomarkers for tumor detection, since they are unique in cancerous cells and are absent in normal and healthy cells. Examples of these recurrent somatic alterations in hematopoietic malignancies usually include the following oncogenic genes: BCR-ABL fusion oncogene, T cell receptor genes, retinoic acid receptor α genes, and immunoglobulin genes (Leary et al., 2010).

A.3. Predictive Biomarkers

Predictive biomarkers provide data about the possible and expected responses to a certain therapy. The biomarkers can provide a plan for a specific treatment. Predictive biomarkers are an anticipation of possible responses the body of the patient will have to the given treatment and how they can affect or improve it. These biomarkers guide the customized treatment plan for patients while getting more information about the malignancy and behavior of the tumor in analysis. Predictive biomarkers are sometimes shared between various tumor types. These predictive biomarkers might be of use in dose determination and selection studies as well as in response measurements of new biological agents. Examples of highly studied DNA biomarkers are the

mutations in gene protein encoders responsible for DNA damage repair. Oncogenes such as the breast cancer gene 1 (BRCA1), and the breast cancer gene 2 (BRCA2) can increase the risk of patients for breast cancer. Some common predictive biomarkers for selected cancers are summarized in Table 1.

Table 1. Summary of predictive biomarkers for selected cancers (taken from Kamel et al., 2017).

Cancer	**Biomarker**	**Clinical utility and significance**
Breast cancer	PR	High PR expression predicting beneficial response to tamoxifen therapy
	ER	High Cellular ER expression predicting benefit from tamoxifen-based chemotherapy in node-negative patients
	BRCA1	High *BRCA1* expression predicting response to chemotherapy
	HER2	Overexpression of *HER2* predicting response to treatment with trastuzumab
	AKT kinase isoform	Akt kinase isoforms and activity predicting response to trastuzumab-based therapy in HER2-positive metastatic cancer patients
Colorectal cancer	LOH at 18q	Predicting benefit from 5-FU based adjuvant chemotherapy
	EGFR1	*EGFR1* amplification predicting response to anti-EGFR1 antibody therapy
	KRAS	*KRAS* mutation negatively predicting benefit from EGFR-targeted therapy
Non-small cell lung cancer	*BRCA1*	High *BRCA1* expression predicting resistance to chemotherapy
	TP53	High *TP53* expression predicting sensitivity to cisplatin; *TP53* mutations predicting resistance to cisplatin

	KRAS	*KRAS* mutation predicting lack of response to adjuvant chemotherapy in early disease and resistance to treatment with EGFR-targeted or TKI in advanced disease

III. Discussion

A. The Role of MicroRNA Expressions in Cancer

Molecular biology provides the technology to develop and identify biomarkers, which are used in therapies such as RNA/DNA microarray tests that help to rationalize and personalize treatment plans (Crommelin, 2011). MicroRNA (miRNA) expression is a gene expression which has received much attention from researchers not because of its great advancement in scientific knowledge, but because they can be adjusted and used in many types of cancer as they are a gene expression that has a direct relation and interaction with the tumor causing the cancer (Mathe et al., 2017). MicroRNAs are fragments of small non-coding RNA that work to regulate gene expression at translational or post-transcriptional levels. MicroRNAs have important interactions with specific oncogenes in various types of cancers. For example, the development of a lymphoma is induced by miR-17, miR-20, and miR-92 microRNA clusters (Mathe et al., 2017). In addition, the overexpression of miR-106a is linked with the downregulation of RB1, a tumor suppressor, in lung, gastric, and prostate cancers (Kamel et al., 2017). MicroRNA's regulate the expression of both the ERα and ERβ receptors. The expression, transcriptional activity, proliferative action of ERα, and the tumor-suppressor properties of ERβ affect the carcinogenic activity of estrogen that usually develops into breast cancer. In ERα-negative cancer cells, the expression of the miRNA-206 increases, which targets the ERα mRNA 3'-untranslated regions (3'-UTR) inhibiting its expression. The microRNA, miR-27a, also inhibits ERα transcription by targeting the repressor of a specificity protein, ZBTB10, which regulates ERα expression (Mathe et al., 2015).

B. Targeted Gene Therapies for Cancer

B.1. Breast Cancer

Breast cancer is classified into four distinct classes based on the profiling of its gene expressions defined by a class of known molecular biomarkers (Sommer, 2001). The classification is summarized in Table 2. Breast cancer is the resulting of carcinogenic activity of estrogen (i.e., estrone, estradiol, and estriol) induced by the proliferative action of ERα through transcription, and by the tumor-suppressor properties of ERβ (Guiu et al., 2009; Perou et al., 2009; Sotiriou & Pusztai, 2009). One of the biological effects of estrogen is the mediation of both the binding and activation of the ERα and ERβ receptors. The ERα and ERβ receptors are classified under the superfamily of nuclear receptor transcription factors, which are classified by its DNA- and ligand-binding domains (Duong et al., 2006).

Table 2. Types of breast cancer based on gene expression profiling (taken from Kamel et al., 2017).

Classification	**Classification**
Luminal-A	Estrogen receptor positive, low histological grade
Luminal-B	Estrogen receptor positive, high histological grade
Basal-Like	Estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2 (HER2) negative
HER2-Like	HER-2 positive and overexpresses erb B-2

Both Luminal-A and Luminal-B cancer show to have an increased expression and elevated levels of genetic biomarkers like those found in the normal breast myoepithelial cells (i.e., luminal cytokeratin). The proliferation of mammary cells induced by estrogen resulting to overexpression, disruption of cell cycle, and cell apoptosis is what characterizes ER-positive breast cancers. ER-positive breast cancers comprise around 80% of the total breast cancer cases. Hormonal therapy helps patients to inhibit the proliferation of cancer cells.

Breast cancer falls into classification of one of five molecular classes. 1, and 2 are luminal A and luminal B (hormone receptor positive). 3 is HER2-positive, a human epidermal growth factor receptor-2. Category 4 is basal-like and normal-like based on microarray and gene expression profiling and 5 claudin-low, triple-negative breast cancer, which includes medullary and metaplastic differentiation (Jeibouei et al., 2019).

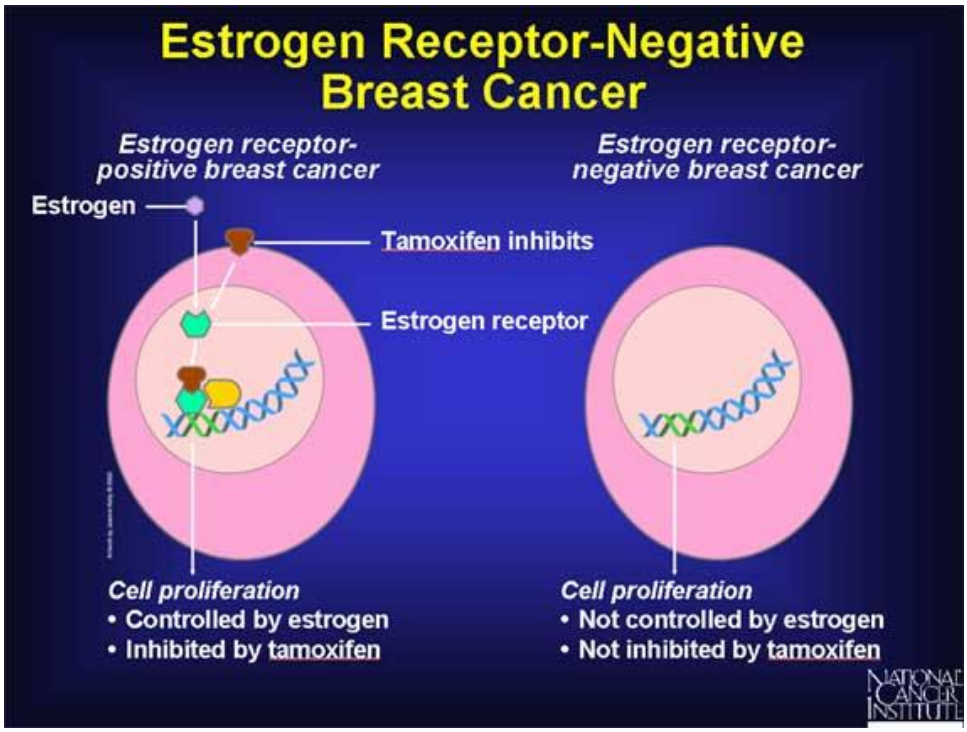

Figure 3. The estrogen-positive and estrogen-negative breast cancer

(taken from the National Cancer Institute, 2020).

An example of a drug administered under endocrine therapy for this type of cancer includes tamoxifen, a selective estrogen receptor modulator, which functions as an antagonist to inhibit the transcriptional activity of the ER receptors (American Cancer Society, 2020). Tamoxifen, a drug commonly used for hormone-positive breast cancer, blocks estrogen attachment to the ER receptors that dampen, or ultimate stop the cancer cell growth (National Cancer Institute, 2020; Sneha & Doss, 2016).

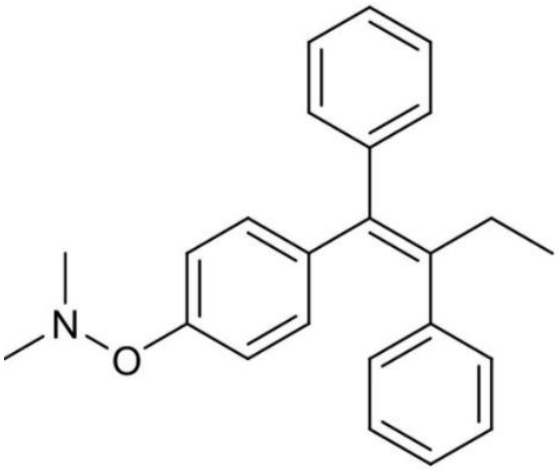

Figure 4. Chemical structure of tamoxifen. (Taken from Valny et al., 2016)

The basal-type cancers, on the other hand, do not overexpress the above-mentioned genes, but they correlate with other biomarkers like cytokeratin 5, epidermal growth factor (EGF), hepatocyte growth factor (HGF), insulin growth factor (IGF)receptors. Statistics show that most breast cancers induced by BRCA1 mutations were of basal-like cancer classification (Kamel et al., 2017).

The ligand-induced activation of the ER receptor starts with the binding of the agonists to the ER complex which induces a series of conformational changes in the receptor leading to the

dissociation of the chaperone protein, the heat shock protein 90 (hsp90), and the dimerization of the ER complex. The co-activator complex then binds to the dimerized receptor, which allows it to interact with the target DNA sequence. Then, the basal transcription factors interact with the attached co-activator complex which stimulates the acetylation of histones and the initiation of the transcription of the target gene. Histone modification reactions prior to transcription are necessary to transform the tightly coiled chromatin into a loose, and transcriptionally active structure. In addition, histone acetylation is an essential part of the ER activation process as histone deacetylase (HDAC) inhibitors can restore the transcriptional activity of the ERα receptor in ERα-negative breast cancer cells. In addition, HDAC inhibitors, as well as various available demethylating agents, serve as an effective treatment for ERα-negative breast cancer patients to induce the expression of the ERα receptor (Ogryzko et al., 1996). The entire transcription process of the ERα gene generates a 4.3 kb long mRNA sequence, which contains the 3'-UTR. This untranslated region contains various regulatory elements that may direct mRNA destabilization (Sommer, 2001).

The antagonist-induced inhibition of the ER receptor, on the other hand, starts with the binding of the antagonist to the ER complex leading to the conformational changes distinct to those found in agonist binding, the dissociation of the hsp90 protein, and the dimerization of the ER complex (Sommer, 2001). The co-suppressor complex then binds to the dimerized receptor, which allows it to interact with the target DNA sequence. However, DNA binding does not recruit all the basal transcription factors leading to the inhibition of the transcription process (Sommer, 2001). Lastly, the co-suppressor complex deacetylates the histones through the action of HDAC, which prohibits the binding of the transcription factors into the tightly wrapped DNA around the histone cores (Sommer, 2001).

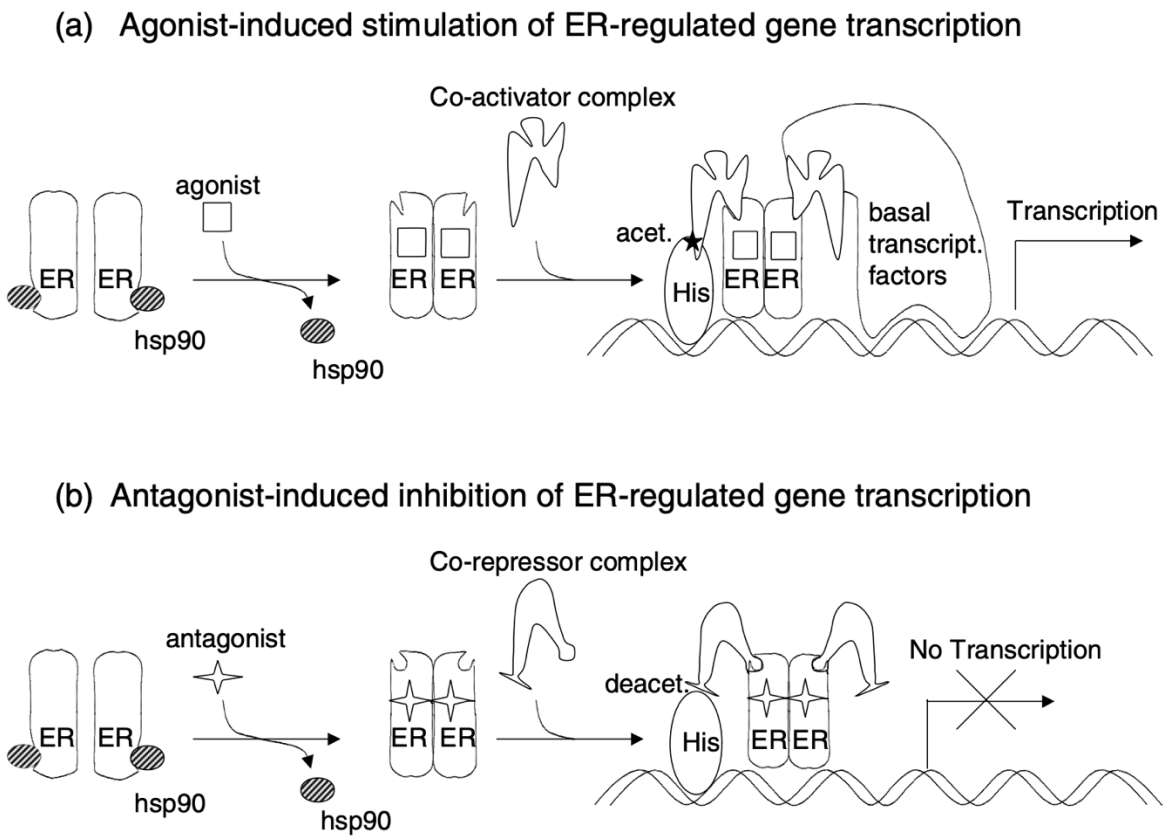

Figure 5. A simplified model of the agonist-induced stimulation and antagonist-induced inhibition of the ER-regulated gene transcription (Taken from Sommer, 2001).

B.2. Colorectal Cancer

Up to this date, there is a scarcity in information about the molecular alterations and gene translocations associated with colorectal cancer. Studies have shown that the progression of this type of cancer involves mutations of the genes that encode the Kirsten rat sarcoma (KRAS) viral oncogene, adenomatous polyposis coli (APC) protein, and the P53 or TP53 tumor protein. In addition, gene expression profiling studies have shown that the 23-gene signature can be a potential predictor for the recurrence of colorectal cancer amongst patients. These findings may help future

researchers in formulating appropriate gene therapies for colorectal cancer patients (Kamel et al., 2017).

B.3. Prostate Cancer

Prostate cancer is one of the leading causes of mortality in men. Even if treatment seems to cure the cancer in its early stages, up to 50% of patients regress after initial therapy (Kafka et al., 2020). Studies show that the initiation and proliferation of prostate cancer cells catalyze from the deletion of the phosphatase and tensin homolog on chromosome 10 (PTEN), which is an essential gene responsible for tumor suppression. The translocation of the genes that encode the E-twenty-six specific related gene (ERG) and the serine 2 (TMPRSS2) transmembrane protease also contributes to the advancement of prostate cancer (Kamel et al., 2017).

B.4. Lung Cancer

In lung cancer there is a 5-gene and 12-gene signature gene expression pattern that correlates with the recurrence of lung cancer among patients after treatment. The 12-gene signature is used to classify patients according to susceptibility to adjuvant chemotherapy (Kamel et al., 2017). A variety of lung cancer biomarkers help to dictate therapy, such as targeting tumor growth by specific drug therapies (EGFR, ALK, ROS1, HER2, BRAF/MEK, MET, and RET mutation and aberrancies) (Sears et al., 2020)

C. Targeted Drug Therapy and Specific Gene Targets: HER2 and EGFR genes

The aim of personalized medicine and targeted drug therapy is to provide a customized treatment plan for patients according to the molecular profiles and signature expression of tumor

tissues. Trastuzumab is a monoclonal antibody used as an adjuvant therapy for HER2-positive metastatic breast cancer patients (Hurvitz et al., 2013). It induces the downregulation of the HER2 gene which is overexpressed in the early stages of the breast cancer. It also acts as a tyrosine kinase inhibitor in colorectal cancer and chronic myelogenous leukemia patients. In addition, trastuzumab inhibits the expression of the EGFR gene in EGFR mutation induced lung cancer. Lapatinib, on the other hand, is a drug that targets the HER2 and possesses a high affinity for the EGFR gene, specifically in the EGFR1 intracellular domains (Hurvitz et al., 2013; Kamel et al., 2017). It is also a tyrosine kinase inhibitor that, in conjunction with trastuzumab, remediates the progression of the invasive HER2-positive breast cancer. Other drugs and targeted therapies for selected types of cancer are summarized in Table 3, Figure 3, and Appendices A-C.

Table 3. Summary of targeted therapies for selected types of cancers (taken from Kamel et al., 2017).

Target	Drug	Cancer type and uses of targeted therapy	Predictive biomarker
HER2	Trastuzumab	First-line or adjuvant therapy for HER2-positive metastatic BC patients	Overexpression of *HER2*
	Pertuzumab	First-line therapy for HER2-positive metastatic BC patients	Amplification of *HER2*
HER2; EGFR	Lapatinib	HER2-positive metastatic BC patients ER, PR, and HER2 triple positive postmenopausal BC patients	Overexpression of *HER2* HR-positive and HER2-positive
EGFR	Cetuximab	EGFR-positive metastatic CRC patients	EGFR protein expression
	Panitumumab	Metastatic CRC patients on chemotherapy and EGFR-positive CRC patients	Wild-type *KRAS*
	Gefitinib	NSCLC patients with *EGFR* mutations	EGFR-activating mutations
	Erlotinib	First-line therapy for metastatic NSCLC patients with *EGFR* exon 19 deletions or exon 21 mutations	*EGFR* deletion or mutation
ALK	Ceritinib	*ALK*-positive NSCLC patients progressing during or after treatment with crizotinib	*ALK* rearrangement
ALK	Crizotinib	*ALK*-positive locally-advanced or metastatic NSCLC patients	*EML4-ALK* translocation

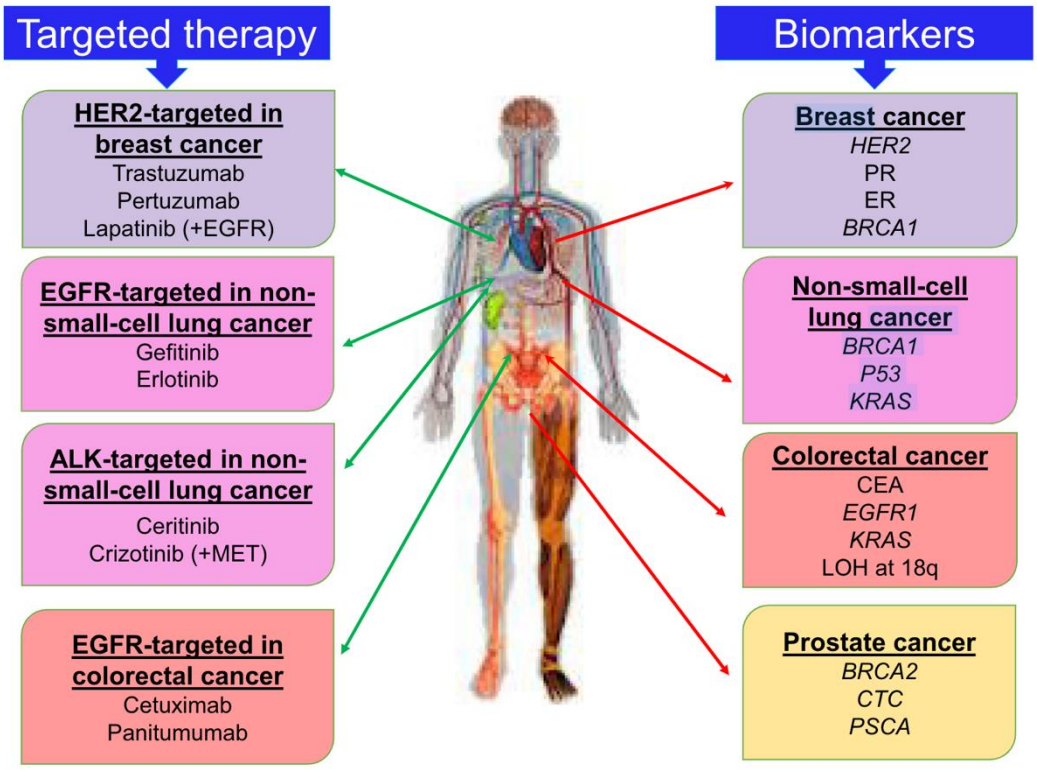

Figure 6. Body map of the available markers and targeted therapies for cancer (taken from Kamel et al., 2017).

Amidst all the advantages presented on personalized medicine, this emerging field also has a list of limitations which can be source of future potential research to further the knowledge on cancer and how it can be treated. Such limitations include the unique genomic profiling of each patient. These small mutations in the genomic sequence can drive the development of medication in cohorts based on the frequency of these genomic alterations. In addition, challenges in validation and implementation of drug combinations, as well the deployment of technologies for DNA sequencing can limit the scope of the study. Further research needs to probe on the development of advance genomic algorithms which can implement high accurate and reliable software that can be used for personalized medicine.

IV. Conclusion

Personalized medicine is a futuristic and potentially idealistic system to help every patient seek for and obtain urgent, specialized attention. It could change the approach to medicine, as well as the attention given to a patient with cancer, specifically attending to the issues the person is presenting and the cancerous cells the patient has in the respective body part. Biomarkers in the therapy for cancer patients could be a helpful tool to provide an on-time prognosis and treatment of the disease. It is also a futuristic plan that cancer patients should have the option to consider. Targeted therapy could also be a transformative change in medical attention, as the use of biomarkers in this therapy can identify the specific type of therapy the patient needs.

V. Appendix:

A. Drug & Gene Table

This table covers 38 drugs undergoing study as gene treatment for 5 different cancers: Breast cancer, colorectal cancer, leukemia, non-small cell lung cancer, and prostate cancer. These drugs for targeted gene therapy were chosen from the National Cancer Institute, 2020.

With these 38 drugs, 17 genes are being targeted for treatment to solve the issue within the gene, causing cancer. They are classified into 13 different types of molecules. To determine which drug would be used for treatment, it should first be determined which gene has gone wrong. From there, a drug that treats the issue of that gene can be decided on.

B. Animated Flowcharts

These flowcharts are simple visual depictions of the drug & gene table spreadsheet located in Appendix A. Each section is separated by cancer type, further branching into the

applicable treatments. Drugs that share a common gene target are grouped together. The flowchart gives more detail about each oncogene: the type of molecule, which chromosome it is located on, the issue leading to cancer, and the gene's function.

C. Illustrations

These illustrations explain targeted cancer treatments in a simplified way.

Image 1: *The switching of pre-cancerous proto-oncogenes into cancerous Oncogenes.*

This image shows genes forcibly turning on the cancer switch, due to the function of oncogenes.

Image 2: *Ways that the expression of some key oncogenes can be lessened.*

This image conveys a group of oncogenes seeking therapy to treat their abnormalities.

Image 3: *Learning about different drugs for treating specific oncogenes.*

This illustration describes the specific treatment for the abnormality in the gene, mTOR, and prescribes specialized drug treatment.

Image 4: *Diagnosing a specific gene abnormality and prescribing treatment.*

In this image, Gleevec is prescribed to treat the abnormality in the gene, BCR-ABL1. The abnormality can lead to Leukemia, and Gleevec treats it by inhibiting protein kinase.

VI. References

American Cancer Society. “Hormone Therapy for Breast Cancer”. 2020. https://www.cancer.org/cancer/breast-cancer/treatment/hormone-therapy-for-breast-cancer.html. Date Accessed: July 01, 2020.

Biomarkers Definitions Working Group, et al. "Biomarkers and surrogate endpoints: preferred definitions and conceptual framework." Clinical pharmacology & therapeutics 69.3 (2001): 89-95.

Chan, Isaac S., and Geoffrey S. Ginsburg. "Personalized medicine: progress and promise." Annual review of genomics and human genetics 12 (2011): 217-244.

Collins, Francis S., Michael Morgan, and Aristides Patrinos. "The Human Genome Project: lessons from large-scale biology." Science 300.5617 (2003): 286-290.

Crommelin, Daan J.A., Gert Storm, and Peter Luijten ‘Personalised medicine’ through “‘Personalised medicines’: Time to integrate advanced, non-invasive imaging approaches and smart drug delivery systems” International Journal of Pharmaceutics Volume 415, Issues 1–2, 30 August 2011, Pages 5-8 doi:10.1016/j.ijpharm.2011.02.010

Duong, Vanessa, et al. "ERa and ERb expression and transcriptional activity are differentially regulated by HDAC inhibitors." 2006

Ganesalingam, Jeban, and Robert Bowser. "The application of biomarkers in clinical trials for motor neuron disease." Biomarkers in medicine 4.2 (2010): 281-297.

Guiu, S., et al. "Molecular subclasses of breast cancer: how do we define them? The IMPAKT 2012 Working Group Statement." Annals of oncology 23.12 (2012): 2997-3006.

Guo, Zhen, et al. "Identification of diagnostic and prognostic biomarkers for cancer: Focusing on genetic variations in microRNA regulatory pathways." Molecular Medicine Reports 13.3 (2016): 1943-1952.

Gwin W.R., Disis M.L., Ruiz-Garcia E. (2019) Immuno-Oncology in the Era of Personalized Medicine. In: Ruiz-Garcia E., Astudillo-de la Vega H. (eds) Translational Research and Onco-Omics Applications in the Era of Cancer Personal Genomics. *Advances in Experimental Medicine and Biology*, vol 1168. Springer, Cham

Hamburg, Margaret A., and Francis S. Collins. "The path to personalized medicine." New England Journal of Medicine 363.4 (2010): 301-304.

Hua, Hui, et al. "Mechanisms for estrogen receptor expression in human cancer." Experimental hematology & oncology 7.1 (2018): 1-11.

Hurvitz, Sara A., et al. "Current approaches and future directions in the treatment of HER2-positive breast cancer." Cancer treatment reviews 39.3 (2013): 219-229.

Jain, Kewal K. "Personalized medicine." Current opinion in molecular therapeutics 4.6 (2002): 548.

Jariyal, Heena, Frank Weinberg, Abhinav Achreja, Deepak Nagarath, and Akshay Srivastava1 "Synthetic lethality: a step forward for personalized medicine in cancer" *Drug Discovery Today* Volume 25, Issue 2, February 2020, Pages 305-320

Jeibouei S, Akbari ME, Kalbasi A, Aref AR, Ajoudanian M, Rezvani A, Zali H. "Personalized medicine in breast cancer: pharmacogenomics approaches" *Pharmgenomics Pers Med*. 2019;12:59-73 https://doi.org/10.2147/PGPM.S167886

Kafka, Mona, Iris E.Eder, Helmut Klocker, and Isabel Heidegger "Emerging promising biomarkers for treatment decision in metastatic castration-resistant prostate cancer"

Urologic Oncology: Seminars and Original Investigations. 2020; https://doi.org/10.1016/j.urolonc.2020.05.025

Kamel, Hala Fawzy Mohamed, and Hiba Saeed A. Bagader Al-Amodi. "Exploitation of gene expression and cancer biomarkers in paving the path to era of personalized medicine." Genomics, proteomics & bioinformatics 15.4 (2017): 220-235.

Knight, William A., et al. "Estrogen receptor as an independent prognostic factor for early recurrence in breast cancer." Cancer research 37.12 (1977): 4669-4671.

Leary, Rebecca J., et al. "Development of personalized tumor biomarkers using massively parallel sequencing." Science translational medicine 2.20 (2010): 20ra14-20ra14.

Mathe, Andrea, Rodney J. Scott, and Kelly A. Avery-Kiejda. "MiRNAs and other epigenetic changes as biomarkers in triple negative breast cancer." International journal of molecular sciences 16.12 (2015): 28347-28376.

Moreno-Sánchez, Rafael, et al. "Understanding the cancer cell phenotype beyond the limitations of current omics analyses." The FEBS journal 283.1 (2016): 54-73.

National Cancer Institute (a). Understanding Estrogen Receptor/SERMs. 2020. http://www.ubooks.pub/Books/ON/B0/E18R1818/TOC.html. Date Accessed: July 01, 2020.

National Cancer Institute (b). Targeted Cancer Therapies. 2020. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet. Date Accessed: July 02, 2020

Ogryzko, Vasily V., et al. "The transcriptional coactivators p300 and CBP are histone acetyltransferases." Cell 87.5 (1996): 953-959.

Perou, Charles M., et al. "Molecular portraits of human breast tumours." nature 406.6797 (2000): 747-752.

Sears, Catherine R., Mazzone, Peter J "Biomarkers in Lung Cancer" *Clinics in Chest Medicine* Volume 41, Issue 1, March 2020, Pages 115-127 https://doi.org/10.1016/j.ccm.2019.10.004

Sneha, P., and C. George Priya Doss. "Molecular dynamics: new frontier in personalized medicine." Advances in protein chemistry and structural biology. Vol. 102. Academic Press, 2016. 181-224.

Sommer, Stephanie. "Fuqua SAW." Estrogen receptor and breast cancer. Cancer Biol 11 (2001): 330-352.

Sotiriou, Christos, and Lajos Pusztai. "Gene-expression signatures in breast cancer." New England Journal of Medicine 360.8 (2009): 790-800.

Valny, M., Honsa, P., Kirdajova, D., Kamenik, Z., & Anderova, M. (2016). Tamoxifen in the mouse brain: Implications for fate-mapping studies using the tamoxifen-inducible cre-loxP system. Frontiers in Cellular Neuroscience, doi: http://dx.doi.org.ezproxylocal.library.nova.edu/10.3389/fncel.2016.00243