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Review

Making Biomarkers Relevant to Healthcare Innovation and Precision Medicine

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Abstract: Translational medicine, the exchange between laboratory (bench) and the clinic (bedside), is decidedly taking on a vital role. Many companies are now focusing on a translational medicinal approach as a therapeutic strategy in decision making upon realizing the expenses of drug attrition in late-stage advancement. In addition, the utility of biomarkers in clinical decision and therapy guidance seeks to improve the patient outcomes and decrease wasteful and harmful treatment. Efficient biomarkers are crucial for the advancement of diagnoses, better molecular targeted therapy, along with therapeutic advantages in a broad spectrum of various diseases. Despite recent advances in the discovery of biomarkers, the advancement route to a clinically validated biomarker remains intensely challenging, and many of the candidate biomarkers do not progress to clinical applications, thereby widening the innovation gap between research and application. The present article will focus on the clinical view of biomarkers in a reverse design, addressing how a biomarker program should appear if it is expected to create an impact on personalized medicine and patient care.

Keywords: precision medicine; personalized medicine; translational medicine; biomarkers; clinical trials; cancer; companion diagnostics; therapy

1. Introduction

The notable advances in genomics and proteomics in the last few decades, and the remarkable advancement in the usage of genome expression evaluation to analyze molecular data from patients have completely transformed the precision medicine field [1,2]. L.J. Lesko, the ex-FDA/CDER appointee, when asked rhetorically if personalized medicine was an "*elusive dream or imminent reality*", replied that it comprised both, "*The elusive dream is to eventually have a treatment custom matched for you, as a patient, based on the individual's*

genetic profile, demographics, and environmental factors. The imminent reality is that we are not there yet". Therefore, precision medicine may be observed more clearly as a prospective and comprehensive strategy in prevention, diagnosis, treatment, and also in tracking diseases in ways that help to obtain optimum, distinctive healthcare outcomes.

1.1. Convergence of Biomarkers, Translational Research, Personalized Medicine, and Future Healthcare

Biomarkers (BMs) are described as biological macromolecules or physiological parameters impartially measured to act as a marker or indicator of a normal or pathogenic cascade [3–5]. A strong aid in designing personalized disease management is the validation and recognition of disease-distinct biomarkers [6,7]. The concept of personalized healthcare, especially aiming at medical intervention on the basis of novel biomarkers, is aptly regarded to influence the healthcare future significantly [3–5]. It depicts a repetitive expansion in evolution in the field of medicine towards a gradually differentiated evaluation of both patients and diseases on the basis of the use of biomarkers with novel characteristics, which are progressively becoming accessible as a result of the recent progress in "*omics*" technologies [3–5]. Current development in biomarker analysis, medical informatics, and biocomputing, along with biotechnology, have amplified new opportunities in the flourishing fields of precision medicine and predictive medicine

Biomarkers have been hailed as one of the solutions to the drug development "pipeline problem". The use of novel biomarkers that promise to make drug advancement a more effective and cost-efficient process is relatively a new idea [8,9]. In 2004, as few as 8% of medical compounds entering Phase 1 trials reached the market, while earlier this figure had been as high as 14% [10]. Studies indicate that biomarkers contribute to the saving of drug development costs by up to USD 100M per project by improving only 10% of decision making and reducing R&D timelines by 3–4 years. Whilst it is difficult to predict the future impact of biomarkers on drug discovery, it is estimated that biomarkers are currently being used in around 15% of drug development programs, particularly in oncology research (Figure 1). However, by 2011, more than 50% of the programs utilized biomarkers as the routinely applied technology in drug development demonstrating utility growth and importance to the drug development process. Table 1 shows a cancer medication labels list that has been amended by the FDA to include information regarding pharmacogenomic biomarkers. A comprehensive list of all biomarkers used in the different therapeutic areas within FDA-approved drug labeling is shown in Table S1.

Table 1. Pharmacogenomic oncology biomarkers in drug labeling | FDA.

Drug	Biomarker	Labeling Sections
Abemaciclib	ESR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Studies
Abemaciclib	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Ado-Trastuzumab Emtansine	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alectinib	ALK	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alpelisib	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alpelisib	ESR (Hormone Receptor)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alpelisib	PIK3CA	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Anastrozole	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies
Arsenic Trioxide	PML-RARA	Indications and Usage, Clinical Studies
Atezolizumab	CD274 (PD-L1)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies

Table 1. *Cont.*

Drug	Biomarker	Labeling Sections
Atezolizumab	Gene Signature (T-effector)	Clinical Studies
Atezolizumab	EGFR	Indications and Usage, Clinical Studies
Atezolizumab	ALK	Indications and Usage, Clinical Studies
Avapritinib	PDGFRA	Indications and Usage, Dosage and Administration, Clinical Studies
Avelumab	CD274 (PD-L1)	Clinical Studies
Belinostat	UGT1A1	Dosage and Administration, Clinical Pharmacology
Binimetinib	BRAF	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies
Binimetinib	UGT1A1	Clinical Pharmacology
Blinatumomab	BCR-ABL1 (Philadelphia chromosome)	Adverse Reactions, Clinical Studies
Bosutinib	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies
Brentuximab Vedotin	ALK	Clinical Studies
Brentuximab Vedotin	TNFRSF8 (CD30)	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Brigatinib	ALK	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Busulfan	BCR-ABL1 (Philadelphia chromosome)	Clinical Studies
Cabozantinib	RET	Clinical Studies
Capecitabine	DPYD	Warnings and Precautions, Patient Counseling Information
Capmatinib	MET	Indications and Usage, Dosage and Administration, Clinical Studies
Ceritinib	ALK	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies
Cetuximab	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Cetuximab	RAS	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies
Cisplatin	TPMT	Adverse Reactions
Cobimetinib	BRAF	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Crizotinib	ALK	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Crizotinib	ROS1	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Dabrafenib	BRAF	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Dabrafenib	G6PD	Warnings and Precautions, Adverse Reactions, Patient Counseling Information
Dabrafenib	RAS	Dosage and Administration, Warnings and Precautions
Dacomitinib	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Dasatinib	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies
Denileukin Diftitox	IL2RA (CD25 antigen)	Indications and Usage, Clinical Studies
Dinutuximab	MYCN	Clinical Studies

Table 1. *Cont.*

Drug	Biomarker	Labeling Sections
Docetaxel	ESR, PGR (Hormone Receptor)	Clinical Studies
Durvalumab	CD274 (PD-L1)	Clinical Pharmacology, Clinical Studies
Duvelisib	Chromosome 17p	Clinical Studies
Enasidenib	IDH2	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies
Encorafenib	BRAF	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Encorafenib	RAS	Dosage and Administration, Warnings and Precautions, Clinical Studies
Enfortumab Vedotin-ejfv	NECTIN4	Clinical Studies
Entrectinib	ROS1	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Entrectinib	NTRK	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Erdafitinib	FGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies, Patient Counseling Information
Erdafitinib	CYP2C9	Use in Specific Populations, Clinical Pharmacology
Eribulin	ERBB2 (HER2)	Clinical Studies
Eribulin	ESR, PGR (Hormone Receptor)	Clinical Studies
Erlotinib	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Everolimus	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Everolimus	ESR (Hormone Receptor)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Exemestane	ESR, PGR (Hormone Receptor)	Indications and Usage, Dosage and Administration, Clinical Studies
Fam-Trastuzumab Deruxtecan-nxki	ERBB2 (HER2)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Fluorouracil	DPYD	Warnings and Precautions, Patient Counseling Information
Flutamide	G6PD	Warnings
Fulvestrant	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Fulvestrant	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Gefitinib	EGFR	Indications and Usage, Dosage and Administration, Clinical Studies
Gefitinib	CYP2D6	Clinical Pharmacology
Gemtuzumab Ozogamicin	CD33	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Gilteritinib	FLT3	Indications and Usage, Dosage and Administration, Clinical Studies
Goserelin	ESR, PGR (Hormone Receptor)	Indications and Usage, Clinical Studies
Ibrutinib	Chromosome 17p	Indications and Usage, Clinical Studies
Ibrutinib	Chromosome 11q	Clinical Studies
Ibrutinib	MYD88	Clinical Studies
Imatinib	KIT	Indications and Usage, Dosage and Administration, Clinical Studies

Table 1. *Cont.*

Drug	Biomarker	Labeling Sections
Imatinib	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Imatinib	PDGFRB	Indications and Usage, Dosage and Administration, Clinical Studies
Imatinib	FIP1L1-PDGFRA	Indications and Usage, Dosage and Administration, Clinical Studies
Inotuzumab Ozogamicin	BCR-ABL1 (Philadelphia chromosome)	Clinical Studies
Ipilimumab	HLA-A	Clinical Studies
Ipilimumab	Microsatellite Instability, Mismatch Repair	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies
Ipilimumab	CD274 (PD-L1)	Indications and Usage, Dosage and Administration, Use in Specific Populations, Clinical Studies
Ipilimumab	ALK	Indications and Usage, Adverse Reactions, Clinical Studies
Ipilimumab	EGFR	Indications and Usage, Adverse Reactions, Clinical Studies
Irinotecan	UGT1A1	Dosage and Administration, Warnings and Precautions, Clinical Pharmacology
Isatuximab- irfc	Chromosome 17p	Clinical Studies
Isatuximab- irfc	Chromosome 4p;14q	Clinical Studies
Isatuximab- irfc	Chromosome 14q;16q	Clinical Studies
Ivosidenib	IDH1	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies
Ixabepilone	ERBB2 (HER2)	Clinical Studies
Ixabepilone	ESR, PGR (Hormone Receptor)	Clinical Studies
Lapatinib	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Lapatinib	ESR, PGR (Hormone Receptor)	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Lapatinib	HLA-DQA1	Clinical Pharmacology
Lapatinib	HLA-DRB1	Clinical Pharmacology
Larotrectinib	NTRK	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Lenvatinib	Microsatellite Instability, Mismatch Repair	Indications and Usage, Adverse Reactions, Clinical Studies
Letrozole	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Studies
Lorlatinib	ALK	Indications and Usage, Adverse Reactions, Clinical Studies
Lorlatinib	ROS1	Adverse Reactions
Lutetium Dotatate Lu-177	SSTR	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Mercaptopurine	TPMT	Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology
Mercaptopurine	NUDT15	Dosage and Administration, Warnings and Precautions, Clinical Pharmacology
Midostaurin	FLT3	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Midostaurin	NPM1	Clinical Studies
Midostaurin	KIT	Clinical Studies
Neratinib	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Neratinib	ESR, PGR (Hormone Receptor)	Clinical Studies
Nilotinib	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Nilotinib	UGT1A1	Clinical Pharmacology

Table 1. *Cont.*

Drug	Biomarker	Labeling Sections
Niraparib	BRCA, Genomic Instability (Homologous Recombination Deficiency)	Indications and Usage, Dosage and Administration, Clinical Studies
Nivolumab	BRAF	Adverse Reactions, Clinical Studies
Nivolumab	CD274 (PD-L1)	Indications and Usage, Dosage and Administration, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Nivolumab	Microsatellite Instability, Mismatch Repair	Indications and Usage, Clinical Studies
Nivolumab	EGFR	Indications and Usage, Adverse Reactions, Clinical Studies
Nivolumab	ALK	Indications and Usage, Adverse Reactions, Clinical Studies
Obinutuzumab	MS4A1 (CD20 antigen)	Clinical Studies
Olaparib	BRCA	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies
Olaparib	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Olaparib	ESR, PGR (Hormone Receptor)	Indications and Usage, Clinical Studies
Olaparib	BRCA, Genomic Instability (Homologous Recombination Deficiency)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Olaparib (5)	Homologous Recombination Repair	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Olaparib (6)	PPP2R2A	Clinical Studies
Olaratumab	PDGFRA	Clinical Studies
Omacetaxine	BCR-ABL1 (Philadelphia chromosome)	Clinical Studies
Osimertinib	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Palbociclib	ESR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Studies
Palbociclib	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Panitumumab	EGFR	Adverse Reactions, Clinical Pharmacology, Clinical Studies
Panitumumab	RAS	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies
Pazopanib	UGT1A1	Clinical Pharmacology
Pazopanib	HLA-B	Clinical Pharmacology
Pembrolizumab	BRAF	Adverse Reactions, Clinical Studies
Pembrolizumab	CD274 (PD-L1)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Pembrolizumab	Microsatellite Instability, Mismatch Repair	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Pembrolizumab	EGFR	Indications and Usage, Adverse Reactions, Clinical Studies
Pembrolizumab	ALK	Indications and Usage, Adverse Reactions, Clinical Studies
Pembrolizumab	Tumor Mutational Burden	Indications and Usage, Dosage and Administration, Clinical Studies
Pemigatinib	FGFR2	Indication and Usage, Dosage and Administration, Clinical Studies
Pertuzumab	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Pertuzumab	ESR, PGR (Hormone Receptor)	Clinical Studies
Ponatinib	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies
Raloxifene	ESR (Hormone Receptor)	Clinical Studies
Ramucirumab	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Ramucirumab	RAS	Clinical Studies

Table 1. *Cont.*

Drug	Biomarker	Labeling Sections
Rasburicase	G6PD	Boxed Warning, Contraindications, Warnings and Precautions
Rasburicase	CYB5R	Boxed Warning, Contraindications, Warnings and Precautions
Regorafenib	RAS	Indications and Usage, Clinical Studies
Ribociclib	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Studies
Ribociclib	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Rituximab	MS4A1 (CD20 antigen)	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Rucaparib	BRCA	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Rucaparib	CYP2D6	Clinical Pharmacology
Rucaparib	CYP1A2	Clinical Pharmacology
Rucaparib	BRCA, Loss of Heterozygosity (Homologous Recombination Deficiency)	Warnings and Precautions, Adverse Reactions, Clinical Studies
Sacituzumab Govitecan-hziy	UGT1A1	Warnings and Precautions, Clinical Pharmacology
Selpercatinib	RET	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Talazoparib	BRCA	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Talazoparib	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Tamoxifen	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Tamoxifen	F5 (Factor V Leiden)	Warnings and Precautions
Tamoxifen	F2 (Prothrombin)	Warnings and Precautions
Tamoxifen	CYP2D6	Clinical Pharmacology
Thioguanine	TPMT	Dosage and Administration, Warnings, Precautions, Clinical Pharmacology
Thioguanine	NUDT15	Dosage and Administration, Warnings, Precautions, Clinical Pharmacology
Tipiracil and Trifluridine	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Tipiracil and Trifluridine	RAS	Indications and Usage, Clinical Studies
Toremifene	ESR (Hormone Receptor)	Indications and Usage, Clinical Studies
Trametinib	BRAF	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Trametinib	G6PD	Adverse Reactions
Trametinib	RAS	Warnings and Precautions
Trastuzumab	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies
Trastuzumab	ESR, PGR (Hormone Receptor)	Clinical Studies
Tretinoin	PML-RARA	Indications and Usage, Warnings, Clinical Pharmacology
Tucatinib	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Vemurafenib	BRAF	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Vemurafenib	RAS	Warnings and Precautions, Adverse Reactions
Venetoclax	Chromosome 17p	Clinical Studies
Venetoclax	Chromosome 11q	Clinical Studies
Venetoclax	TP53	Clinical Studies
Venetoclax	IDH1	Clinical Studies
Venetoclax	IDH2	Clinical Studies
Venetoclax	IGH	Clinical Studies

Table 1. *Cont.*

Drug	Biomarker	Labeling Sections
Venetoclax	NPM1	Clinical Studies
Venetoclax	FLT3	Clinical Studies
Vincristine	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Adverse Reactions, Clinical Studies

The table lists 184 oncology biomarkers, as of August 2020. Adapted from Drugs@FDA; https://www.fda.gov/drugs/scienceresearch/ucm572698.htm) (accessed on 27 November 2021). The list includes several types of biomarkers, such as genetic variants, chromosomal abnormalities, altered gene expression, among others.

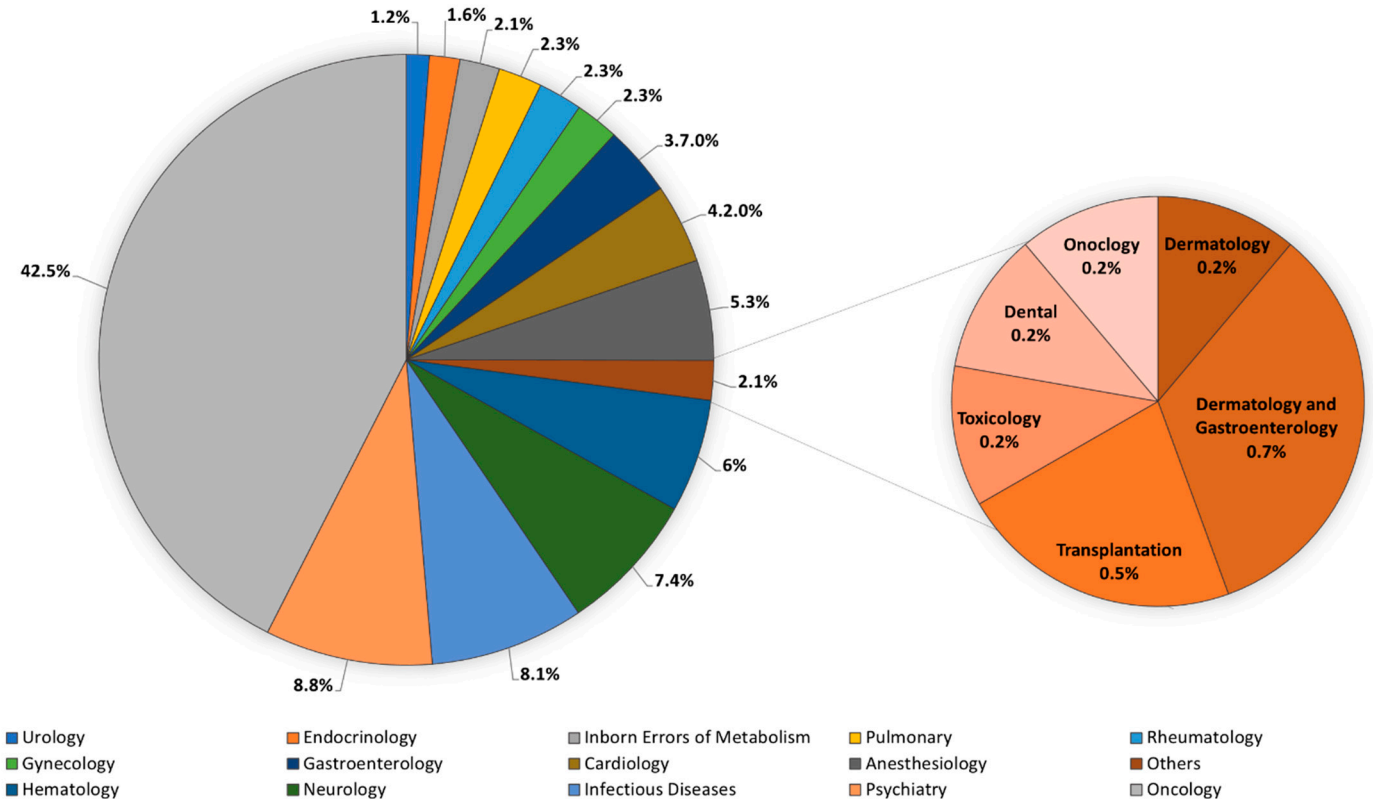

Figure 1. Pharmacogenomic Biomarkers in Drug Labeling Classified According to Field of Study. The figure was created based on data from Drugs@FDA (https://www.fda.gov/drugs/scienceresearch/ucm572698.htm) (accessed on 27 November 2021), as of August 2020. Out of 431 drugs, 42.5% were the field of oncology. A comprehensive list of all biomarkers used in the different therapeutic areas within FDA-approved drug labeling is shown in Table S1. The biomarkers list includes, but are not limited to, germline or somatic gene variants (i.e., polymorphisms, mutations), functional deficiencies with a genetic etiology, altered gene-expression signatures, chromosomal abnormalities, and selected protein BMs that are used to select treatments for patients.

Translational medicine, when practiced properly, attempts to foster closer interactions between R&D segments promoting the advantages of exchanging scientific information between "*bench to bedside*" and "*bedside to bench*". The free flow of information between the clinical and preclinical settings not only capitalizes on scientific advances, but also makes the most effective individualized patient clinical decisions. Precision medicine can be described as the utilization of new techniques of molecular studies to effectively regulate the disease of a patient's susceptibility in development of a disease [11]. The field focuses on achieving optimum medical results by assisting both patients and physicians to select the disease management strategies expected to provide successful outcomes based on the environmental circumstances and unique genetic profiles of the patients [11,12]. Precision medicine stands poised to alter healthcare practice for the upcoming several decades [11]. A large number of new prognostic and diagnostic tools will enhance our

capacity to anticipate the probable results of drug therapy. Further, the extension in the use of biomarkers can lead to favorable clinical outcomes during the drug development process [11–13]. Additionally, it guarantees the probability of enhanced health results and possesses the capacity to make healthcare more cost-efficient.

In summary, several forces are converging today to shape the future of healthcare including the "*omics*" technologies, declining productivity and innovations in drug development, increasing use of biomarkers integrated into drug development programs, patient welfare, in particular drug safety (biomarkers relevance), and US-FDA policies.

1.2. Understanding the Patient through Biomarkers: Brief History and Trends, beyond "Discovery" by Correlation

Biomarkers have a wide range of applications. The wide applicability of biomarkers includes diagnostic tools, patient stratification/triage, and utility in evaluating response to treatment, in assessing staging of disease advancement, and determining safety to signify toxicity and ill effects [4,5] (Figure 2). The utilization of biomarkers is not a novel concept; in fact, they have been used for diagnostic and prognostic purposes for centuries [14]. With the advent of routine laboratory testing, the notion of using diagnostic testing to guide therapy has been firmly established in medical practice. For instance, diabetics measure their sugar levels to ascertain proper insulin doses [9]. The pathologists use phenotypic histological or immunochemical markers in classifying cancers and guiding prognoses including effective therapeutic options. Lastly, the liver function enzymes are tested to identify patients with adverse reactions to statins therapy [15].

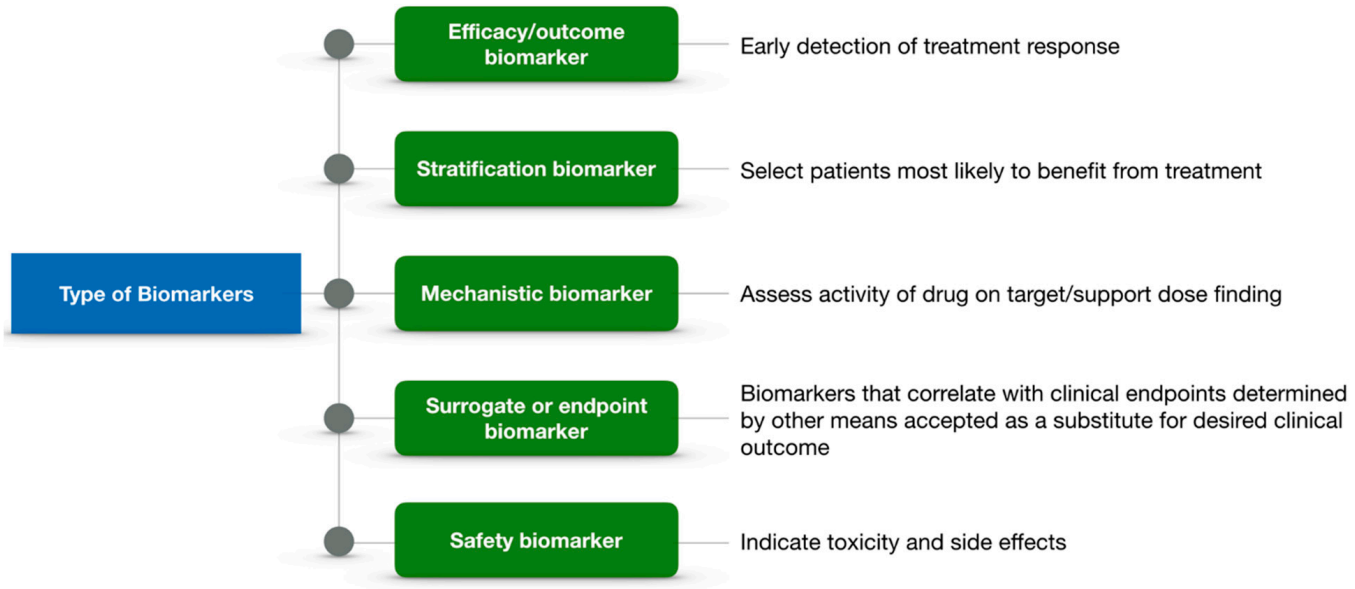

Figure 2. Summary of Biomarker Types and Potential Contexts of Use. The utility range of biomarkers include diagnostic tools (early qualifiers of disease, target recognition), patient identification/triage (e.g., Her-2-Nu positive for treatments with Herceptin®), therapeutic response assessment (mechanistic biomarkers and imaging modalities), disease classification and monitoring, and safety indication toxicity and side effects.

The vast majority of biomarkers fall into one of four categories: small molecules, proteins, genetic markers, or imaging indicators. The FDA has already started to define the qualities of an ideal biomarker. The features are summarized in Figure 3. The FDA preliminary guidelines under deliberation are clear and reasonable; however, the question remains: what technological tactics might be applied to develop pertinent biomarkers? Indeed, several approaches can be utilized. Yet, given the characteristics described, it is essential to focus on the measurement of biophysical reactions and interactions. Possibly,

the best assessment to depend on would be to identify proteins, quantify them, and most importantly, examine the isoforms and interrelate those proteins with the clinical information [16]. Unlike nucleic acids, proteins are secreted into bodily fluids, such as serum or urine, in response to a physiological reaction, thus nullifying the need for a tissue sample. In particular, proteins, and their relative expression and body concentration, as well as their direct connection to genetic, external, and internal influences, signify a perceptible articulation of biological status [16,17]. Proteins are what disease processes have an effect on and are therefore, the inevitable target for drugs. Hence, the technology most appropriate in the above-mentioned context is proteomics [16].

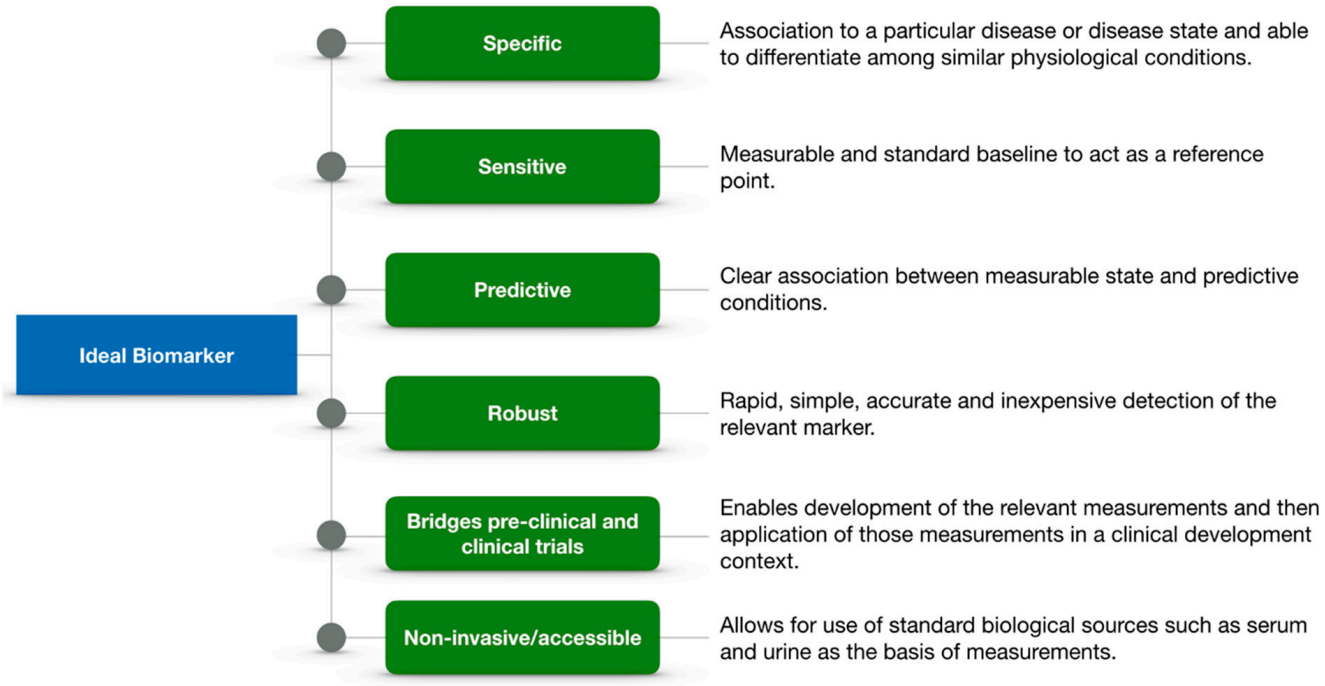

Figure 3. Definition of an Ideal Biomarker. According to the US-FDA, an ideal biomarker should be specific, sensitive, predictive, robust, able to bridge preclinical and clinical trials, and accessible.

1.3. Biomarkers towards Precision Medicine in Cancer

Biomarkers are extremely important in oncology; they are crucial for risk assessment, screening, differential diagnosis, prognosis determination, prediction of disease recurrence and response to therapy, and progression monitoring [6]. With cutting-edge proteomic and genomic technologies, DNA and tissue microarrays, gel electrophoresis, mass spectrometry, and protein assays, as well as improved bioinformatics tools, the evolution of biomarkers to reliably assess the results of cancer mitigation and therapy is now possible. Looking forward, a urine or a serum test for each stage of cancer may possibly drive clinical decision making, complementing, or even replacing presently available invasive methods [6,18].

Cancer therapy is getting more "personalized". Over the last several decades, the identification of oncology-specific biomarkers has become a foremost goal for cancer researchers (Table 1). The common usage of prostate-specific antigen (PSA) in prostate cancer screening has prompted investigators to look for appropriate biomarkers for screening other kinds of cancer. Targeted medicines, such as Iressa® (gefitinib), Gleevec® (imatinib), and Herceptin® (trastuzumab), are currently available and may benefit from a more targeted treatment based on diagnostic testing [19].

Indeed, the importance of biomarkers in anti-cancer therapy research cannot be overstated nowadays. In the clinic, biomarkers may help identify individuals who are most likely to react to a medication, enable real-time monitoring of treatment effectiveness, or detect early indications of drug toxicity. Furthermore, biomarkers are heavily used in

go/no go decision making throughout the drug development cycle, from early discovery to preclinical assessment [16].

1.4. A Perspective on the Role of Biomarkers in Clinical Medicine

The idea of objective indicators has been long practiced in medicine, and biomarkers have been long used in the medical arena for decades. As science progresses and develops, the area of biomarkers as objective indicators of processes has spread and grown [16,20]. In the context of clinical medicine, biomarker-related processes may be divided into six groups: (i) Risk assessment biomarkers: to assess the risk of a disease evolution; (ii) Screening biomarkers: to screen for subtle subclinical illnesses; (iii) Diagnostic biomarkers: to objectively differentiate between the subjective diagnostic perceptions of physicians; (iv) Staging biomarkers: to identify and monitor the staging and severity of illnesses; (v) Predictive biomarkers: to foresee a potential course of disease; (vi) Personalizing biomarkers: to select personalized biomarkers, which is plausible with the advances in genomics technology and other "*omics*" [21,22]. The roles of biomarkers in precision medicine are thus becoming more and more valuable, diverse, and incalculable. Patient stratification for clinical trials and treatment selection ought to minimize risk and maximize potential benefit [23,24]. The right selection of patients is foundational to evidence-based clinical medicine as to "who should be treated, how and with what" [23,24]. They represent essential elements to enable the vast diversity in personalized medical trials such as the N = 1 trials that might be conducted via recruiting a number as small as one subject into the trial [23,24].

2. Applications of Biomarkers in Precision Medicine

2.1. Prevention and Early Intervention

A precedent in the above-mentioned area is to screen for *BRCA1* and *BRCA2* polymorphisms, which signify a genetic predisposition to breast and ovarian cancers [25]. Women with *BRCA1* or *BRCA2* have about 40–87% and 27–84% odds of developing breast cancer, respectively [26–35]. While for ovarian cancer, women with certain *BRCA1* or *BRCA2* gene mutations have a 16% to 60% and 11% to 27% likelihood of disease, respectively [28,33,36–38]. Indeed, the above tests may guide preventative actions, including prophylactic surgical intervention and chemoprevention.

2.2. Optimum Therapy Selection

Each person is unique in his/her genome and predisposition for diseases. The idea is that the "*one drug fit for all*" approach is leading to therapy failure or drug toxicity. Typically, a marketed drug works on an average for only 50% of the people who take it. According to a report, the percentages of patients for whom a particular drug is ineffective were 38% for antidepressants, 40% for asthma drugs, 43% for anti-diabetic drugs, 50% for anti-arthritis drugs, 70% for Alzheimer drugs, and 75% for anti-cancer drugs (Figure 4) [39]. Application of the concept of optimal therapy selection paves the way for stratified medicine (also known as, precision medicine or personalized medicine) [40]. The ramifications in terms of care cost and quality of care are considerable. The use of biomarkers permits the physician to choose an optimum therapy at the outset and circumvent the exasperating and costly practice of trial-and-error prescription. The most universal example given is *HER2*, which is used to identify the 25% to 30% of breast cancer patients who will benefit from receiving Herceptin® (trastuzumab). In metastatic colon cancer, about 40% of patients are doubtful to respond to two drugs, Erbitux® (cetuximab) and Vectibix® (panitumumab), due to mutations in their *KRAS* gene. Clinical practice guidelines recommend that those patients with only the *KRAS* gene normal form should be treated with these drugs in conjunction with chemotherapy.

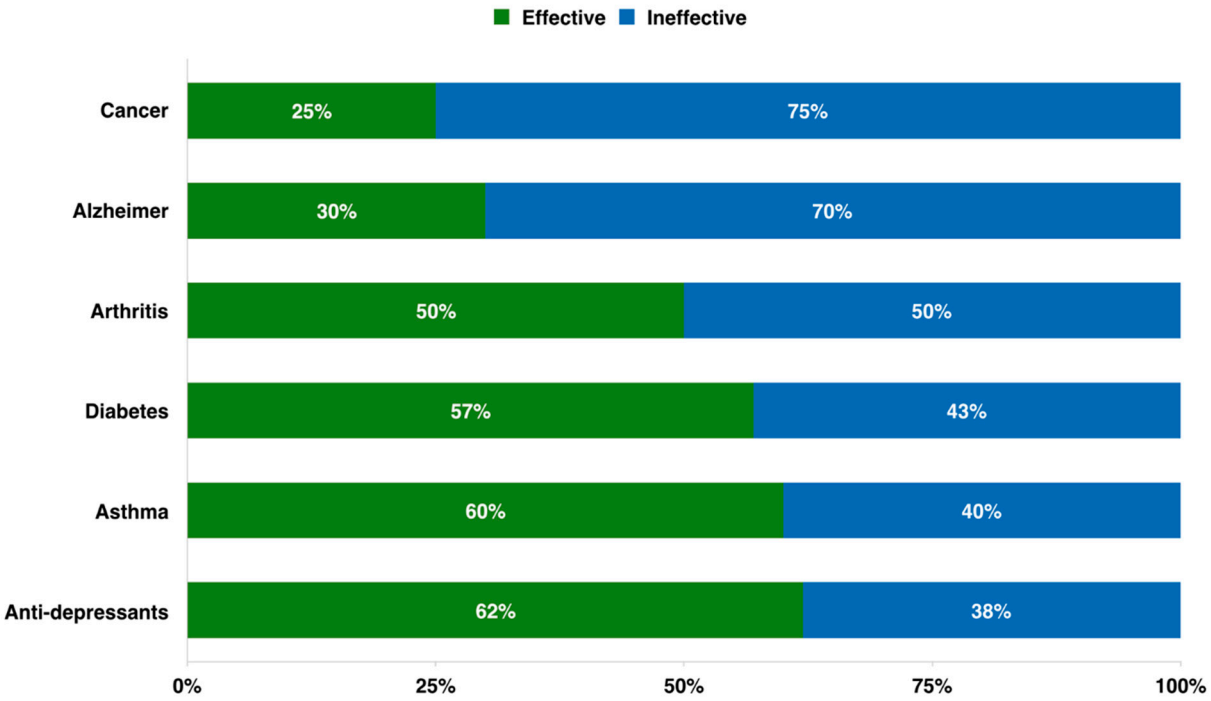

Figure 4. Estimate of Ineffective Drug Responses. Estimates show that 75% of anti-cancer drugs, 70% of Alzheimer drugs, 50% of anti-arthritis drugs, 43% of anti-diabetic drugs, 40% of asthma drugs, and 38% of antidepressants are ineffective. Adapted from [39].

2.3. Drug Safety

Adverse drug reactions (ADRs) represent a serious consequence to patients. ADRs hospitalization is nearly 5.3% of admissions. Numerous ADRs are the results of genes coding for variations in the cytochrome P450 (CYP450) family of enzymes and other metabolizing enzymes. For instance, the FDA-approved Amplichip® CYP450 test helps clinicians make informed decisions regarding therapy options and drug dosages. Another FDA-approved example is the UGT1A1 assay™, which measures variations in the liver enzyme UDP-glucuronosyltransferase. The test predicts patients' safety-related responses to Camptosar® (Irinotecan), which is a standard colon cancer treatment. The assay permits clinicians to alter the drug dosage for roughly 10% of the patients who metabolize the active form of the drug too slowly, where its accumulation in turn would lead to toxicity.

2.4. Patient Compliance

Non-compliance of patients during treatment results in, not only adverse health effects, but also increased costs. Patients are more inclined to comply with their therapy armed with knowledge and confidence. Personalized treatments, once proven to be more effective and/or present fewer side effects, will automatically encourage compliance. The above could be seen in treatments of other conditions such as diabetes or asthma, where non-compliance often makes it worse.

2.5. Improvement Rate of Success of Clinical Trials

The patient stratification strategy ensures drug validation success during clinical trials. Using biomarker testing in clinical trials, scientists may first choose individuals for study inclusion based on their anticipated benefit from the therapy and/or their susceptibility to negative side effects. Enriching the clinical trial pool will shorten, reduce, and/or lower the cost of clinical trials [40].

2.6. Healthcare Benefit Cost Reduction

Healthcare spending in the U.S. is rising. Over the last few years, the expense of the drug ineffectiveness for hypertensive and cholesterol medications alone has exceeded USD 1.2 billion–USD 3.8 billion. Precision medicine is critical for improving the healthcare system since it resolves issues with things such as untraceable drugs, unnecessary appointments to the hospital, and unsafe medical procedures. Research has been conducted, and it has been shown that personalized treatment creates clear economic advantages. For example, it is possible to save costs significantly by doing patient testing using UGT1A1 assay™ to identify patients who need lower doses of Irinotecan because of potential drug reactions. The study also found that if Vectibix® (panitumumab) or Erbitux® (cetuximab) were provided to metastatic colorectal cancer patients with the wild type *KRAS* gene, who are the only ones to get the benefits of the medicines, the country could save USD 604 million a year.

Another cost management example illustrates the power of Artificial Intelligence (AI). During the American Society of Hematology Annual Meeting (59th ASH), GNS Healthcare jointly with the Multiple Myeloma Research Foundation (MMRF) reported on their AI platform findings. The team found a biomarker that could qualify multiple myeloma patients' stem cell transplantation eligibilities to guarantee benefit from the operation. AI analysis of 645 multiple myeloma patients identified the putative biomarker, CHEK1, which determines a patient's response to stem cell treatment. Patients with low gene dosage received a 22-month Progression Free Survival (PFS) benefit from the operation while patients with high gene dosage did not receive any significant benefits. Discovering the link between a cancer patient's genetic profile and treatment response ahead of undergoing a costly, invasive operation, such as stem cell transplantation, highlights the role of precision medicine in the making of difficult medical decisions in high-risk diseases.

3. Therapeutic Treatment and Biomarkers

The developments of personalized therapies and diagnostic tests are conducted simultaneously to provide essential data regarding the safe and effective use of a corresponding therapeutic treatment which is defined as companion diagnostics (CDx) by the US FDA [41,42]. The FDA has approved sixteen oncology medicines for 32 CDx tests from 1998 to 2016. The first approved CDx was Herceptin® which was introduced in early 1998 to treat breast cancer patients with HER-2/neu (Figure 5) [43–45]. The CDx tests are used for precise treatments that employ either small molecule inhibition of intracellular tyrosine kinase activity or monoclonal antibody inhibition of ligand-induced receptor activation.

Recently, two new CDx tests have been approved for cancer. The first drug is for patients with an aggressive and rare type of leukemia, i.e., AML with FLT3 mutation, and represents the new first treatment for this type of leukemia over two and half decades as the overall survival was significantly improved (23% reduction in the risk of death) [46–48]. The other CDx test is for advanced ovarian cancer patients, and it was the first drug that does not require BRCA mutation or other biomarker testing. Further, it is expected that around 15% of ovarian cancer patients would benefit from the BRCA analysis test.

A paradigm shift in the "*one test, one drug model*" is taking place that has defined CDx. More recently, Quest Diagnostics has collaborated with ThermoFisher Scientific to commercialize the company's next-generation sequencing (NGS)-based CDx panel for non-small cell lung (NSCL) cancer, which was given FDA approval in June 2017. In total, the panel investigates 23-genes, and can determine whether an individual has one of three FDA-approved treatments-linked gene mutations, including those in EGFR, ROS1, and BRAF. Not only that, but it can examine whether or not additional variations exist in other genes. Oncomine Dx Target Test can be employed as a CDx for AstraZeneca's EGFR inhibitor Iressa® (gefitinib), Pfizer's ALK and ROS1 inhibitor Xalkori® (crizotinib), and a combination of trametinib (Novartis' MEK inhibitor Mekinist®) and dabrafenib (RAF inhibitor Tafinlar®). In November 2017, FoundationOne CDx (F1CDx) received FDA approval for a 324-gene NGS-based test that detected genetic changes that are associated

with several types of cancer including melanoma, colon cancer, breast cancer, ovarian cancer, and neuroendocrine tumors. F1CDx kit also offers information on the instability of microsatellites and the mutational burden of the tumor.

About 75% of the targeted and immune-oncology investigational therapies in development depend upon diagnostics to support their clinical end points and demonstrate response. The rationale of deploying a diagnostic in an oncology drug development is to mitigate risk, nevertheless, if not managed properly, a CDx can instead add significant risk to regulatory approval of novel oncology drugs. Thus, the CDxs have been shown to be vital tools in advance drug development due to: (1) fast and high chances of regulatory approval; (2) cost reduction, i.e., most suitable patients for a particular treatment (stratification of patient population).

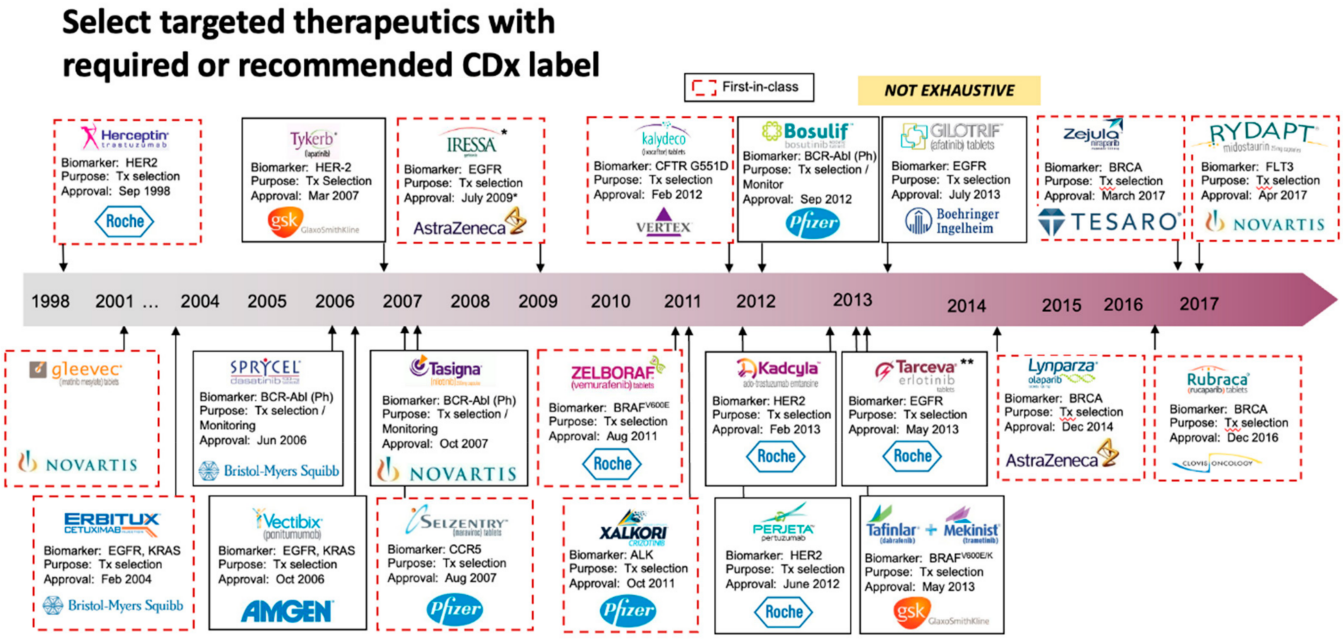

Figure 5. Overview of List of Approved Oncology CDx Tests on the Market. The first approved CDx was Herceptin® which was introduced in early 1998 to treat breast cancer patients with HER-2/neu. The CDx tests are used precisely for specific therapies that inhibit signal transduction pathways by either inhibiting the intracellular tyrosine kinase activities using a small molecule or preventing ligand-induced receptor activation with a monoclonal antibody.

4. Treatment: Current Guidelines and Opportunities for Novel Tests by Working within the Existing Frameworks

A clinical biomarker in oncology might be used to accomplish the following: (i) for early detection, that is early diagnosis of symptomatic patients and screening of healthy population to identify asymptomatic individuals; (ii) as a prognostic biomarker to objectively assess the patient's overall outcome independent of treatment; (iii) to evaluate delivery of medicine to target/tumor; (iv) to evaluate impact of medicine on target/tumor; (v) to determine impact of drug on patient; (vi) as a predictive biomarker to objectively assess the potential impact of a particular therapeutic intervention or the differences in intervention results; (vii) as a surrogate endpoint for efficacy.

5. Clinical Research: Information-Based and Adaptive Protocols through Biomarker Testing

Precision medicine trials to evaluate a biomarker-targeted therapy face challenges when a large number of patients are required for rare diseases or for polygenic diseases such as schizophrenia, for example. It is further complicated by a need for efficiency to answer more questions, such as mechanistic means in less time. Internationally coordinated

efforts by consortia are some of the innovative methodologies to address such complex issues. While being able to recruit thousands of patients and controls, they adopt a strategy to employ master overarching protocols to answer multiple questions in the shortest time possible.

A methodological innovation receptive to the aforementioned entails evaluating multiple treatments in more than one subject type or disease within the same overall clinical trial structure. Such design is alluded to as master protocol; defined as one overarching protocol intended to answer several questions. Several targeted treatments for a single illness, a single focused therapy for multiple diseases, or various target treatments for numerous disease characteristics may all be investigated using this approach.

6. Regulatory Approval and Availability of Physician Use and Patient Access

The advanced development of new therapeutic agents specially with targeting a certain biomarker and then finding its off-label efficacy in other diseases have added to the pressure on patients, physicians, and regulatory agencies.

Patients in situations where standard of care treatments fail usually adopt "a clinging to straw" approach and would chase any hope if it was an experimental drug. In turn, physicians are put under pressure to expand access to compassionate medicine and at times, with no proven evidence. In response to these pressures, regulatory agencies are easing regulations on off-label drug use. Typically, this would involve an emergency IND, Investigational New Drug, request to allow a voluntary release of the drug by the manufacturer. Regulating such access is governed by four principles: (i) anticipation, which includes needed planning, resources, staffing, supply, and policies for access requests; (ii) accessibility, which accounts for transparency and ease of finding contact information and access policies for all parties involved; (iii) analysis, which is concerned with data (access request and outcomes) collection, tracking, and review; (iv) accountability of procedures in charge such as those responsible for execution during the defined period for access requests and closed-loop communications.

The strategies to evaluate biomarkers extend beyond analyzing the scientific studies to determine the full acceptance of a biomarker. It is noteworthy to mention that the suggested framework for evaluating biomarkers will provide consent on whether or not a biomarker is suitable. In doing so, the framework gives context-dependent and context-independent standards as well as testing for analytical validation. Analytical validation is a significant component of the biomarker validation process to ensure robust supporting data prior to deployment. Performance method stringency is critical to the "*fit-for-purpose*" validation strategy. Furthermore, it is pivotal to know the prognostic value of the biomarker, and whether the complete mechanism underlying the disease is clearly elucidated. Additionally, the evaluation of the biomarkers needs to be updated regularly to reflect the current status of the scientific research.

Most notably, it is suggested that the information required to make policy choices regarding biomarkers must also be precise for all product categories and intended applications. Lastly, while evaluating the biomarkers for nutrition-associated uses, it is necessary to utilize the indicators with respect to the food or supplement metabolism or intake.

7. Clinical Utilization: Uptake Trends and Challenges in Impacting Clinical Medicine

Generally, biomarker research often goes through a series of stages that begins with discovery and concludes with clinical application. Figure 6 gives a representation of the biomarker pipeline. The pipeline development of a biomarker generally constitutes four main phases. The process starts with a screening stage that involves assessing a low number of samples, followed by analyzing hundreds to thousands of samples for the clinical evaluation of the biomarker being studied [17]. Effective incorporation of biomarker investigations in oncology clinical trials necessitates: (i) an unambiguous and convincing hypothesis, which is dependent on a strong rationale backed by evidence-based research,

(ii) a well-established assay, sample handling protocol, and data analysis/assessment, and (iii) a properly designed and executed clinical trial.

The focus in biomarkers work is currently on clinical application in two main areas: translation and personalized medicine. Translating the accumulated research knowledge into intrasignaling information and signaling pathways allow for the developing of targed drugs. Precision medicine, on the other hand, and the stratification of diseases allow for the defining of what treatment, at what dose, and at what time should it be provided to the particular patient. However, the trend in biomarkers work has been revolving about the workplace of scientists, diagnostics, and advanced technologies. With current globalization, outsourcing research work to more cost-effective places, such as China, Russia, India, and Brazil, is becoming the trend in research involving biomarkers. The shift is also revolving around identifying biomarkers with diagnostic, prognostic, and disease-burden quantification values. Furthermore, advanced technologies such as NGS, mass spectrometry, and imaging genetics are affecting the landscape of biomarkers discovery/development and their impact on human disease.

The trends and advances in precision medicine have not passed unchallenged. Several challenges thus exist in preventing the biomarkers from occupying their full potential. Firstly, in medical service laboratories, there are still insufficient accepted robust tests to detect biomarkers for clinic use. Further, data analyses of analyzed biomarkers are also not yet well-developed to meet user-friendly standards needed for most clinicians and scientists.

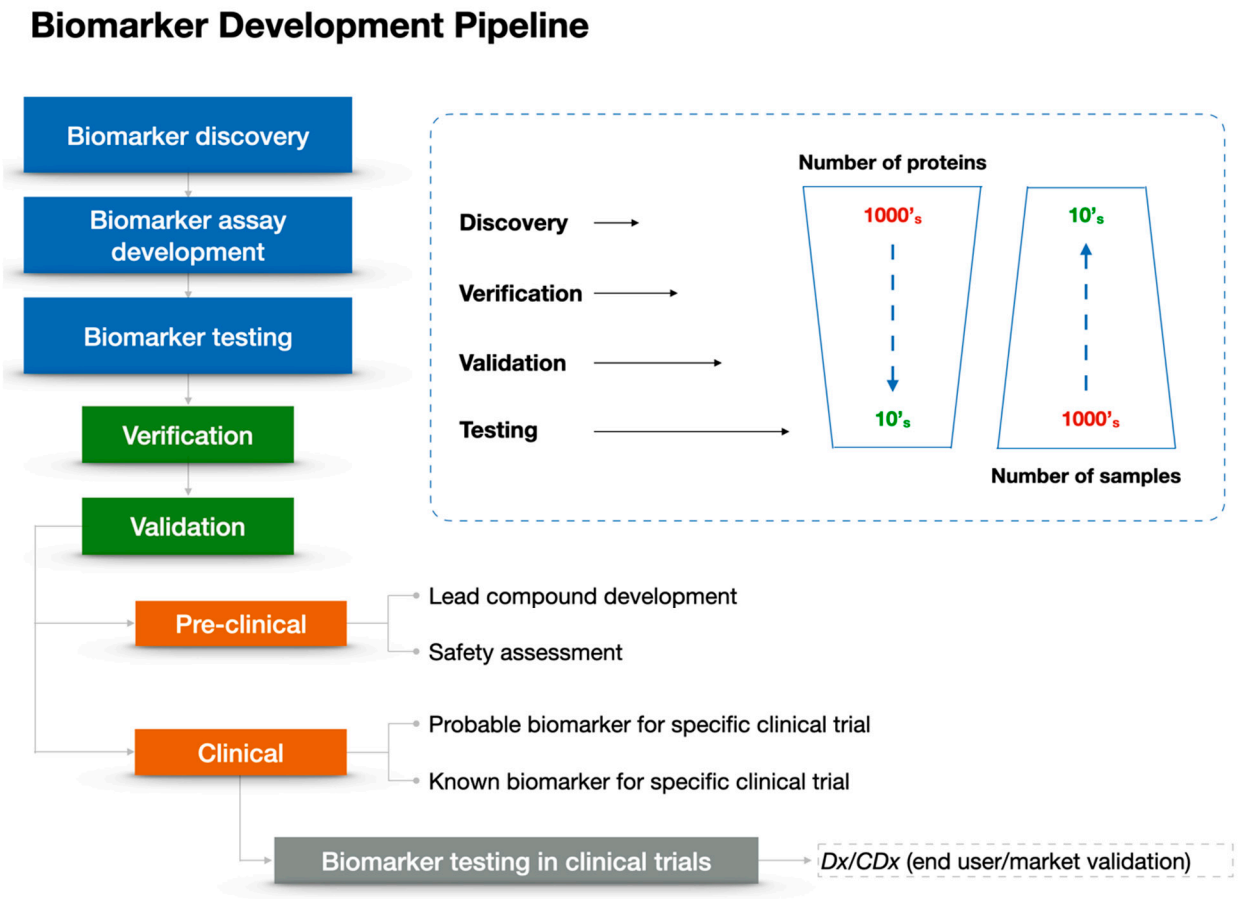

Figure 6. A Schematic of the Biomarker Pipeline. The main phases in the pipeline are presented including biomarkers discovery, verification, and validation stages. In addition, typical numbers of candidate biomarkers passing through each phase are indicated, highlighting the foregoing enigma, wherein, despite our capacity to generate long lists of candidates, only few make it to the final stages. Additionally, this illustrates the value of reverse biomarkers design process.

8. Application of Biomarkers and Surrogate Endpoints in Clinical Efficacy Analysis and Formation of Clinical Practice Guidelines

Surrogate endpoints have been used in approving products or claiming for foods, devices, biologics, drugs, and supplements including clinical practice guidelines formulation. In 1990, The "*Institute of Medicine (IOM) committee*" said, "*practice guidelines are systematically developed statements to help the practitioner and patient decisions about appropriate health care for specific clinical circumstances*". A guideline with respect to therapy of a specific disease might recognize the target levels for particular biomarkers. To reach approval for the levels of a specific biomarker, the data obtained from clinical trials and observational studies have to be evaluated. It is anticipated that a large number of trials might calculate a specific surrogate endpoint in comparison to the targeted clinical endpoint. In such situations, it is preferred to add dossier from trials which do not calculate the targeted clinical endpoints in the systematic reviews.

Additionally, other techniques for accurate, systematic reviews such as the Cochrane Collaboration might be useful in evaluating the evidence correlated with the guidelines for clinical practice. One proposal, that bodies associated with the determination of the foremost guidelines for clinical practice, is to make it cost-effective. The topic of cost effectiveness is considered by the committee as being beyond the statement of task for the current study as well as the studies conducted elsewhere.

The engagement of professional societies is crucial in allowing the stakeholders to leverage their deep knowledge of biomarkers and learn about the best opportunities to utilize biomarkers in the clinics. Another valuable way is the dissemination of the guidelines for clinical practice by these societies to enhance the utility and comprehension of biomarker data.

The extensively considered use of surrogate endpoints is in phase III of clinical trials to support new regulatory submissions. In a public workshop, Dr. Robert Temple of the Center for Drug Evaluation and Research (CDER) at the FDA presented a summary of the rationale behind the use of surrogate endpoints by the clinicians and researchers [49]. The reasons are as follows: when there is a direct link between the surrogate endpoints and the clinical endpoint of interest; when the clinical endpoint is infrequent or takes unusual time to develop; when the other therapy exists to confront obstacles in organizing trials; when to prove a new intervention is superior to available therapies [50]. Additionally, it might be likely to utilize a clinical endpoint in a high-risk population for certain diseases; however, analyzing a population at comparably lower risk level utilizing the clinical endpoint represents a burden due to the requirement of a very large number of subjects [50]. The idea of a surrogate endpoint is to enable a nimbler clinical trial that is smaller, faster, and more efficient, which can contribute to the immediate requirements and facilitate the advancement of medicine and therapy.

9. Oncotype DX and Mamma/BluePrint Tests for Breast Cancer

Women diagnosed with localized breast cancer face difficulties in making decisions with their doctors regarding the kind of neoadjuvant (before surgery) treatment, deciding whether or not chemotherapy is required after surgery, and of any specific chemotherapy medications to be used. Numerous molecular tests have been designed to address the foregoing issues and the options for testing are also increasing. Tests are oriented towards diverse patient populations and few are more entrenched than the others. Currently, Oncotype DX is perhaps the most frequently used test in the USA to make decisions for breast cancer treatment. The National Comprehensive Cancer Center Network (NCCN) provides clinical guidelines for the Oncotype DX [51]. However, this test is applicable only for women who are estrogen receptor (ER)-positive, that is during the early stage of breast cancer. Hence, it is of irrelevant use for women with ER-negative cancers [51]. Moreover, Oncotype DX distinguishes tumors in terms of risk factors by interpreting the 21 selected gene expressions in tumor biopsies and assists in the determination of the requirement for chemo- or radiotherapy after the surgical removal of the tumor [51]. A

"numerical recurrence score" (1 to 100) is used by the test that differentiates tumors into three categories: low risk (0–17), intermediate risk (18–30), or high risk (≥31) of recurrence.

Oncotype DX was independently endorsed by two studies [52,53]. The prospective NSABP-B14 research affirmed the recurrence score (RS) as a stable recurrence predictor, independent of age and tumor size [52]. The NSABP B-20 study found evidence that recurrence scores may potentially be used to predict which patients with ER-positive, node-negative cancer would benefit the most from adjuvant chemotherapy, in terms of disease-free survival and overall survival in comparison to endocrine treatment alone [53].

Paik et al. estimated the Kaplan–Meier score of distant recurrence at ten years to be 6.8%, 14.3%, and 30.5% for low-, intermediate-, and high-risk patients, respectively. Analysis showed that RS could also accurately predict the recurrence of the disease at ten years, when considered as a continuous variable [52], in comparison to the online adjuvant tool [54]. Further, RS was reported to be an independent predictor of breast cancer-associated mortality in tamoxifen-treated individuals with node-negative disease, ER^+ with a 10-year risk of mortality as 15.5%, 10.7%, 2.8% and in patients categorized as high-risk, intermediate-risk, and low-risk, respectively [53]. However, other available genomic assays reported to possess better predictive values for the disease recurrence at the later onset [55,56]. However, the clinical usefulness in the selection of patients for the adjuvant chemotherapy strategy in comparison to the use of the extended endocrine approach has not been clearly demonstrated. The advantage of adjuvant systemic chemotherapy is to prevent the early disease recurrence [57,58].

As a gene-expression profiling tool, "MammaPrint" is applied to assess the recurrence risk and metastatic spread of breast cancer in patients with early-stage disease, and in turn identifies if the tumors are ER^+ or ER^-. Thus, it has wider relevance than Oncotype DX [59]. MammaPrint is implemented in patients having stage I or II lymph node-negative cancer that are less than 61 years old and have a tumor size less than 5 cm. MammaPrint determines the expression of 70-genes in tumors, which is more when compared with the Oncotype DX measurement. MammaPrint 70-genes signature was chosen in an unbiased way as they were selected by a data-driven strategy from the genome-wide expression data. The MammaPrint genes content apparently totally reflects the six hallmarks of cancer biology. The finding suggests a crosstalk amid the underlying molecular mechanisms and molecular signature of the progression and metastasis of tumor cells [60].

MammaPrint assists in choosing the appropriate treatment type after surgery by classifying tumors as either low- or high-risk. Furthermore, the US-FDA permitted MammaPrint to be used in examining archival tissues (i.e., paraffin-embedded), which might further expand its applicability. It could act as both a predictive and prognostic tool and helps individuals identify the most significant clinical query for the management and care of the breast cancer patients: (i) Who is in danger for recurrence? (ii) Which patient could safely do without chemotherapy? (iii) What is the most advantageous therapy for each patient?

Buyse et al., (2006) conducted a study on 302 patients and reported that MammaPrint showed a statistically significant difference in the probability of metastasis-free survival at 10 years by stratifying patients either into lower or higher risk categories with the help of binary risk classification [61]. Knauer et al., (2010) reported on the predictive value of MammaPrint for adjuvant chemotherapy during the early phase of breast cancer. MammaPrint showed a statistically significant p value ($p = 0.01$) in a statistical separation in distant disease-free survival (DDFS) to the allocated high-risk category patients. The endocrine along with chemotherapy category had an 88% DDFS, while only the endocrine-treated category had a 76% DDFS in the high-risk group. The analysis concluded an overall 50% relative benefit and 12% absolute benefit for the combination group. However, for the low-risk group, no statistically significant benefit was observed for the chemotherapy along with endocrine therapy vs. only endocrine therapy categories [62]. Moreover, the potential of MammaPrint was demonstrated by the RASTER study to possess the capacity to precisely stratify patients with breast cancer into high-risk or low-risk groups in comparison to that of the existing traditional clinical parameters [63]. Recently, the MINDACT

investigation documented the clinical applicability of MammaPrint in comparison to the standard clinical pathological criteria for identifying the patient to rarely benefit from the adjuvant chemotherapy [64].

A new analysis namely BluePrint, which is promoted by Agendia, has the capability to reclassify breast tumors on the basis of "functional" subtypes [65]. BluePrint provides better classification for the subtypes of breast cancer which further guides towards the optimal choice of neoadjuvant therapy [65]. Similarly, it might guide for the selection of neoadjuvant treatment for HER2-positive cancers. Several studies followed the results of neoadjuvant therapy in $HER2^+$ cancers and their association with the test results of BluePrint. As reported by Agendia, BluePrint reclassified around 22% of $HER2^+$ tumors from the initial diagnosis [65]. Within these cancers BluePrint recognized a subtype ("luminal") that appeared to be resistant to neoadjuvant treatment along with chemotherapy and Herceptin®. However, when Pertuzumab (Perjeta®—a newer HER2-targeted drug) was added to the Herceptin®; the luminal subtype showed a better response. The mentioned information also showed that BluePrint could recognize which individual with $HER2^+$ should undergo Perjeta® as part of their neoadjuvant therapy [65,66].

10. Ethnic Disparities in Biomarkers

Developing genomic-based testing that quantifies the risk of cancers and helps understand the tumor profile, offers treatment guidance and management of patients' risk/therapy and thereby, smarter care for patients from diverse ethnic groups. The genomic testing would deliver the promise and value of precision medicine targeting sub-populations with a high risk and the unique biology of every cancer. This is particularly important for breast cancer, which is the most frequently observed cancer among women, globally characterized by having a heterogeneous, highly complex, and multifactorial nature with several documented risk factors contributing to its initiation. Inflammatory breast cancer is a rare cancer type that merely affects 1–5% of patients in the USA [67,68]; nonetheless, is more common in North Africa, accounting for as high as 11% of cases in Egypt [69]. If one can distinguish and recognize the proteins and genes associated with the aggressive form of breast cancer, he/she will be able to delineate the mechanisms associated with the transition from localized and controlled breast cancer to the aggressive form. The present efforts to delineate the Arab genome [70–73] might aid in discovering new ethnic-specific biomarkers. Moreover, the outcomes of the analyses are expected to recognize Arab-specific variants that might play a critical role in the molecular pathology of various diseases, including cancers, and could contribute to identifying significant genotype–phenotype association. The above investigations may feasibly contribute to disease prognosis and management in the future, ultimately, providing a way forward for precision medicine to help to reduce the burden of disease. In the Arab world, particularly in Qatar, this type of knowledge makes a valuable contribution to the drive towards precision health. The State of Qatar has initiated two major projects. The Qatar Biobank (QBB) collects biosamples and health/lifestyle details from the Qatari populace, and The Qatar Genome Program (QGP) is mapping the genome of the resident population [70,71]. Collectively, data would recognize the association of genotype–phenotype pertinent to the Qatari population. Further, a comprehensive Qatari genotyping array, the Q-Chip, has been developed. Development of a second generation of Q-Chip is underway. The new version has more processed clinical content and is designed to satisfy the local health requirements, thus delivering on the commitment of precision medicine for the population which in turn enables the evolution of precision healthcare in Qatar to usher in a new era in patient-centric care [74].

11. Conclusions

A seismic structural modification is taking place in the field of medicine. There is a visible acceleration in the pace of the stepwise processes of discovery, development of the products, and clinical adoption of what one knows as precision medicine. Due to the expanding insight into the correlation between acute disease, biomolecules, and

genomics, and also with the increasing sophistication of diagnostic processes, the interest towards the analysis of biomarkers is at an all-time high. Though there are several research analyses delineating and endorsing the value of the prognostic and diagnostic biomarkers, it is a comparatively budding field in association with the actual translation to the clinic. Biomarkers also play a crucial role during the process of drug advancement from drug discovery and preclinical research to clinical development and diagnostics, including a pivotal role in the development of safer and more efficacious drugs. Biomarkers will form a part of the new "toolkit" that would be needed by the pharmaceutical industry if it is to lower costs and increase the success rate of its new candidates. The significance of the present systems, such as, clinical trial ethics and medical records privacy, healthcare payer and physician incentives must be surveyed by all stakeholders who need to reach an agreement on the alterations that should be made. The way such matters are handled would impact the development of personalized medicine and shape its capability to prevent, diagnose, and regulate disease.

In short, biomarkers and precision medicine have introduced a novel way of thought processes, appraising diseases, in applying novel advanced technologies, and emphasizing proactive and preventive medicines. Biomarkers are providing value across the entire drug development spectrum and the shift is impacting both the patients and the entire landscape of the healthcare system. Biomarker-driven personalized healthcare is a question of "*when*" and not "*if*".

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pr10061107/s1, Table S1. List of pharmacogenomic biomarkers in FDA drug labeling, as of August 2020.

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