

Am J Nucl Med Mol Imaging 2016;6(6):310-327
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0039837

Original Article

Precision medicine and molecular imaging: new targeted approaches toward cancer therapeutic and diagnosis

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Received July 24, 2016; Accepted September 27, 2016; Epub November 30, 2016; Published December 15, 2016

Abstract: This paper presents a review of the importance and role of precision medicine and molecular imaging technologies in cancer diagnosis with therapeutics and diagnostics purposes. Precision medicine is progressively becoming a hot topic in all disciplines related to biomedical investigation and has the capacity to become the paradigm for clinical practice. The future of medicine lies in early diagnosis and individually appropriate treatments, a concept that has been named precision medicine, i.e. delivering the right treatment to the right patient at the right time. Molecular imaging is quickly being recognized as a tool with the potential to ameliorate every aspect of cancer treatment. On the other hand, emerging high-throughput technologies such as omics techniques and systems approaches have generated a paradigm shift for biological systems in advanced life science research. In this review, we describe the precision medicine, difference between precision medicine and personalized medicine, precision medicine initiative, systems biology/medicine approaches (such as genomics, radiogenomics, transcriptomics, proteomics, and metabolomics), P4 medicine, relationship between systems biology/medicine approaches and precision medicine, and molecular imaging modalities and their utility in cancer treatment and diagnosis. Accordingly, the precision medicine and molecular imaging will enable us to accelerate and improve cancer management in future medicine.

Keywords: Precision medicine, molecular imaging, precision medicine initiative, systems biology, metabolomics-based systems medicine, cancer theranostics, radio-omics, P4 medicine

Introduction

President Obama announced in his State of the Union Address on January 20, 2015, “I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes-and to give all of us access to the personalized information we need to keep ourselves and our families healthier” [1, 2]. Now the President has declared a research initiative that aims to accelerate progress toward a new age of precision medicine [1]. Precision (or personalized) medicine is being strongly supported as a solution to selectively target cancer cells and minimize damage to normal tissue [3]. The

goal of this initiative is to acquire momentum of precision medicine [1]. It also aims to identify diagnostic and treatment models whose central focus is on the individual variability of disease presentation [4]. As an inestimable tool in precision medicine, theranostics, which is a portmanteau term of “therapeutics” and “diagnostics”, was coined by John Funkhouser in 2002. It can be defined as a diagnostic methodology for individually tailored therapeutic intervention, and it personalizes healthcare practices to an individual patient by removing inessential treatments for whom a standard therapy is not suitable and/or by optimizing a therapeutic plan for a particular patient [5]. The rapid

growth of precision medicine requires dedicated future leaders with a strong foundation in advanced genomic medicine, including molecular diagnostic techniques such as next generation sequencing and whole genome/exome sequencing interpretation. These leaders should integrate personalized medicine into healthcare, and they must attain many additional management and teaching skills [6]. The electronic medical records (EMRs) and genomic research effort work to advance personalized and precision medicine. In fact, the eMERGE network launched in 2007 is an NIH-funded consortium devoted to genomic discovery and implementation investigation by leveraging biorepositories connected to EMRs [7]. The precision medicine requires information technology (IT) infrastructure for the storage, maintenance, and transfer of large amounts of individual genomic data. With such a biobank IT, the researchers enable the management of genetic data for individual patients and other research [8]. The largest precision medicine project in Germany was launched in 2013, entitled the German National Cohort (GNC). This project is a nationwide, long-term study with an overall duration of 25-30 years and a €210 million budget for the first 10 years. Despite these projects, precision medicine in Germany is still significantly smaller than in the United States [9].

Molecular imaging is quickly acquiring recognition as a tool that has the capacity to improve every aspect of cancer treatments. Molecular imaging in oncology has been described as in vivo characterization and the measurement of key biomolecules and molecularly based events that are fundamental to the malignant state [10]. While molecular imaging is defined by the Society of Nuclear Medicine as the “visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems” [11], the burgeoning demand among physicians, patients, and communities for personalized care is increasing the importance of molecular imaging and forming the development of biomedical imaging as a whole [10]. Molecular imaging is developing to include a variety of imaging techniques to enable in vivo monitoring of cellular and molecular processes [11]. Although molecular imaging has existed for decades, the rapid progress of molecular and

cell biology, imaging technology, and imaging probe evolution have highly raised its power and potential. Essential to the development and translation of molecular imaging is interdisciplinary collaboration across many fields, including radiology, nuclear medicine, pharmacology, chemistry, molecular and cell biology, physics, mathematics, and engineering. In fact, these include positron emission tomography (PET), single photon emission computed tomography (SPECT), computed tomography (CT), MRI, MRSI, ultrasound, and optical imaging [10]. Hence, imaging techniques and system biology approaches can be applied as two high-throughput methods to cancer therapy and diagnosis in clinical experiments.

Cancer is one of the widespread causes of death all over the world. Cancer research has focused on the identification of molecular differences between cancerous and healthy cells [12]. There is much evidence that the interaction and network between genes and proteins plays an important role in the research of cancer molecular mechanisms. It is essential and significant to present a new initiative of precision medicine in cancer investigation by integrating systems biology, clinical science, omics technology, bioinformatics, and mathematical science to improve diagnosis, therapies, and prognosis of diseases [13]. Cancer is disease established on the malfunction of system characteristics in biology. Therefore, it has been recognized as a systems biology disease [12]. Advances in science and technology have provided approaches toward the diagnosis, therapies, and prognosis of cancer such as molecular imaging and systems biology as new targeted methods in clinical science. Systems biology has appeared during the two recent decades as a powerful new pattern for investigation in life science [14]. Our understanding of cancer initiation and progress has been furthered by means of high-throughput discovery technologies, such as next generation sequencing and the core omics including genomics, radiogenomics, transcriptomics, proteomics, and metabolomics [15]. Indeed, those are systems biology approaches for better comprehending of cancer systems biology. This review's purpose is to highlight the role and importance of precision medicine and molecular imaging technologies accompanying systems biology/medicine approaches to cancer therapeutics

and diagnosis to create new targeted approaches in future medicine.

Precision medicine

According to the National Institutes of Health (NIH), precision medicine is “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person” [2, 16, 17]. This approach will permit physicians and investigators to predict more precisely which treatment and prevention strategies for a special disease will work in which groups of people. It is in conflict to a “one-size-fits-all” approach in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals. Although the term “precision medicine” is relatively new, the concept has been a part of healthcare for many years. For instance, a person who requires a blood transfusion is not given blood from a randomly selected donor; instead, the donor’s blood type is matched to the recipient to decrease the risk of complications [1, 2]. Although examples can be found in several areas of medicine, the role of precision medicine in day-to-day healthcare is relatively limited. Scientists hope that this approach will expand to many areas of health in the coming years [16]. Indeed, precision medicine is now widely utilized only in oncology [4], particularly for treatment of melanoma, metastatic lung, breast, and brain cancer and leukemia [18]. Radioiodine theranostics is a typical example of precision medicine and has been utilized widely for the management of differentiated thyroid cancer [5]. Generally, precision medicine has not yet become a medical standard for many conditions in spite of its high expectations in the United States, Germany, and other countries [9].

Difference between precision medicine and personalized medicine

Between the terms “precision medicine” and “personalized medicine”, there is a lot of overlap. According to the National Research Council (United States), “personalized medicine” is an older term with a meaning similar to “precision medicine”. There was concern that the term “personalized” could be misconceived to imply that treatments and preventions are being

advanced uniquely for each individual; in precision medicine, the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors [2, 9, 19]. The Council therefore preferred the term “precision medicine” to “personalized medicine”. However, some people still utilize the two terms interchangeably [16].

Precision medicine initiative

In early 2015, President Obama announced a strong conviction that science and investigation offer great potential for focusing on bringing precision medicine to many facets of healthcare [1, 9, 20]. The President’s budget for fiscal year 2016 comprised of \$216 million in funding for the initiatives of the NIH, the National Cancer Institute (NCI, the NIH institute focused on cancer research), and the Food and Drug Administration (FDA) [9]. The Precision Medicine Initiative has both short-term and long-term purposes. The short-term objectives include enlarging precision medicine in the field of cancer research. Investigators at the NCI hope to utilize this approach to find novel, more effective cares for different types of cancer based on increased knowledge of the biology and genetics of the disease. The long-term objectives of the Precision Medicine Initiative focus on bringing precision medicine to all aspects of health and healthcare on a large scale as well as generate knowledge applicable to the whole range of health and disease [1]. For this goal, the NIH schemes to start a study including a group (cohort) of at least one million volunteers from around the United States. Participants will provide genetic data, biological samples, lifestyle, environment, and other information about their health. This data will be utilized by investigators to examine a large range of diseases, with the aims of better predicting disease risk, comprehending how diseases happen, and finding improved diagnosis and treatment strategies [16].

Systems biology as an efficient tool in precision medicine

The expression “systems biology” has appeared during recent years to explain the frontier of interdisciplinary investigations in biology [21]. The modern biology is supported by the progress in high-throughput experimental techniques such as genomics, transcriptomics, pro-

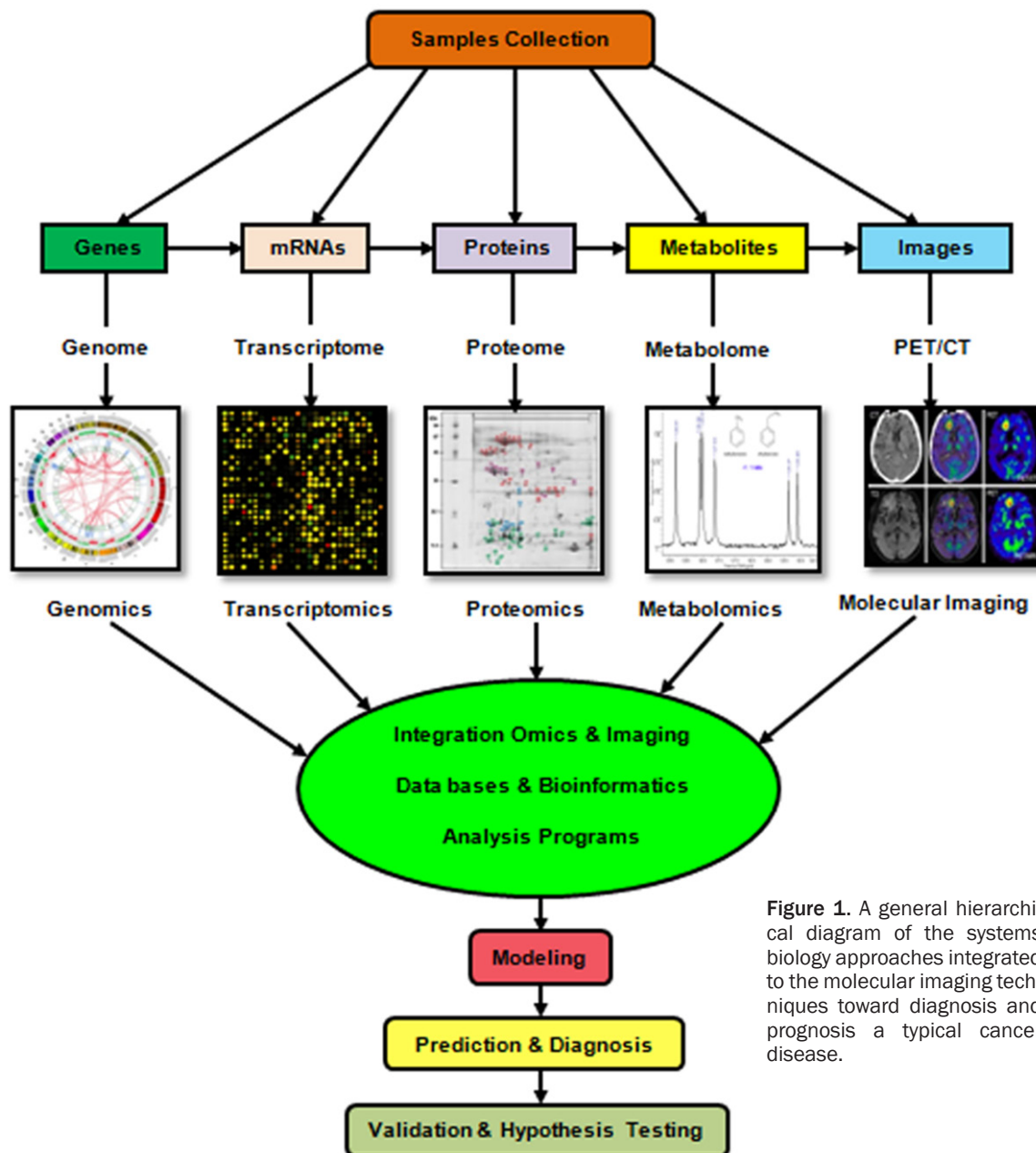


Figure 1. A general hierarchical diagram of the systems biology approaches integrated to the molecular imaging techniques toward diagnosis and prognosis a typical cancer disease.

teomics, metabolomics, phenomics, and other omics technologies that may generate “big data science”. Systems biology has been described as the study of biological components and their interactions using models and/or networks to integrate genes, metabolites, proteins, regulatory elements and other biological components via high-throughput technologies such as DNA-microarray, Fluorescence microscopy, Illumina sequencer, GC-MS, LC-MS, MALDI-TOF, HPLC, FT-IR, mass spectrometry, HPLC-MS, NMR, and so on [22, 23].

Through systems biology, we can find out more puzzling images regarding the fundamental components of biology including the genome, transcriptome, proteome, metabolome, membrane systems, organelles [24, 25]. The big data biology, network biology, and other new branches of modern biology have emerged as a result of the combination of versatile knowledge (Figure 1). For instance, understanding of systems-level of the cell or cellular components and subprocesses will be facilitated by network biology. The aim of systems biology is to com-

Table 1. An overview of the common omics techniques for systems medicine and precision medicine

Technique	Molecules of interest	Description	Temporal variance	Affect by disease status	High-throughput instruments
Genomics	DNA	Evaluation of variability in DNA sequence in the genome	None	No	Illumina sequencing, Pyrosequencer (GS-FLX Titanium), Roche 454 [37, 115]
Transcriptomics	RNA	Evaluation of variability in composition and abundance of the transcriptome	High	Yes	Affx arrays (Illumina sequencing, Roche 454) [37, 115]
Proteomics	Protein	Evaluation of variability in composition and abundance of the proteome	High	Yes	MS, 2DE, iTRAQ [47, 115, 116]
Metabolomics	Small molecules (metabolites)	Evaluation of variability in composition and abundance of the metabolome	High	Yes	NMR, DE-NMR, LC-MS, GC-MS, MALDI, MS [47, 115]

prehend the functions and mechanisms in the different levels of organisms or cells [26]. Today, systems biology is encountering the challenges of analyzing huge biological networks and big molecular biological data.

Systems approaches

It is necessary to integrate experimental and computational research in order to understand complex biological systems. In other words, it is a systems biology approach [27]. Nowadays, the holistic systems biology approaches have created a new outlook in biology, medicine, and pharmacological sciences [28, 29]. Systems biology has provided the base for encoding the structure, variation, and function of the human genome and relating them to health and disease states by high-throughput technologies for DNA sequencing and for analyses of transcriptomes, proteomes, and metabolomes [29]. Many biological processes have already applied omics approaches to lead a large number of genes potentially included in corresponding modules. Development and implementation of computational methods was an important step of progress by which genes or proteins that conduct similarly under different experimental situations [30]. In this section, we discuss on the principal “omics” techniques including genomics, transcriptomics, proteomics, and metabolomics as the most frequently approaches applied in systems medicine research. An overview of the omics technologies for systems medicine and precision medicine has also been presented (**Table 1**).

Genomics and transcriptomics

Evolution in high-throughput technologies has produced a paradigm shift for biological systems in advanced life science investigations.

The systems biology by means of methodically organizing the genomics, functional genomics, and proteomics data attempts to provide a systems-level comprehension of the biological phenomena [31]. In 1986, the term “genomics” was coined by Thomas Roderick for first time. Genomics expression was quickly applied as the novel journal name intended to sustain the new areas and discipline of genome mapping and sequencing [21, 32]. Indeed, this was a big and fantastic transformation in molecular biology through the evolution of dramatically efficient approaches for DNA sequencing [33]. Genomics is the branch of science that studies the genome, or the genetic material or blue print of a plant, animal, human, microorganisms, and/or other species in order to understand the functions, gene interactions, and regulation of gene networks with each other and the environment [34]. Nevertheless, the focus of genomics research is mostly on the investigation of sequencing (sequence genomics), functions (functional genomics), structures, and interactions of genes. An example of a huge international genomics project was the Human Genome Project that was successfully completed in 2003 [21]. One of the first omics technologies that had thereafter developed was transcriptomics [35]. Transcriptomics is defined as the study of transcriptome under particular circumstances or in a certain cell by high-throughput technologies such as RNA-seq and microarray analysis [36]. The most important purposes of transcriptomics are: to make an itemized list of all species’ transcripts, including mRNAs, non-coding RNAs, and small RNAs; to appoint the transcriptional structure of genes in terms of their beginning sites, 5’ and 3’ ends, splicing models, and other post-transcriptional alterations; and to quantify the modifying expression levels of each transcript during evolution and under various situations.

In order to conclude and quantify the transcriptome, various state of the art technologies have been created such as hybridization or sequence-based approaches [37].

Radiogenomics

Radiogenomics is the newest member of omics family. The concept of radiogenomics is the study of the correlation between cancer imaging features and gene expression (Imaging Genomics) and genotypic variations observed in response to radiation therapy (Radiation Genomics) [38]. The combination of imaging tools with molecular techniques (such as functional genomics assays) offers the potential for the quick clinical translation of powerful high-throughput technology [39]. Radiogenomics may create imaging biomarkers that can recognize the genomics of a disease, particularly cancer, without the use of a biopsy [40]. Numerous techniques are applied to reveal correlations between MRI, CT, and PET imaging features and the genomics of disease (such as large-scale MRI microRNA-mRNA correlative study in glioblastoma, liver cancer genome from non-invasive imaging features, and link image characteristics of non-small cell lung nodules in CT scans) to predict survival using gene expression data [39]. In addition, functional CT in oncology and cardiovascular imaging is a key player in the age of precision medicine and radiogenomics [41].

Proteomics

Proteomics, the study of proteomes on a large scale, promises to transform biology and medicine [42, 43]. The study of proteomes in the large scale is defined as proteomics. A proteome is defined as the set of proteins that is generated in a system, organism, or other biological entity. For example, we can refer to the proteome of an organ, such as the liver, or of a species, such as *Homo sapiens*. The proteome changes from cell to cell at any given time; thus, it is not constant [44]. The term “complete proteome” is applied in the field of mass spectrometry (MS)-based proteomics, pointing toward the presently unachieved aim realizing all the proteins of a given species [45]. To investigate proteomes, several high-throughput techniques have been developed, among them mass spectrometry (MS)-based techniques, such as tandem-MS, and gel-based techniques, such as

differential in-gel electrophoresis, which are the most utilized in proteomics. Via these high-performance devices, we can produce enormous amounts of data. Therefore, we require databases for registering, storing, and maintaining these huge amounts of data so that investigators can create links between their outcomes and the available knowledge [44, 46].

Metabolomics

Metabolomics enables the integration and merging of biological data from different levels, revealing communication and connectivity inside a system as a key for precision medicine and phenotyping [47]. Metabolomics is an omics technique in systems medicine that is used in the global quantitative evaluation of endogenous metabolites in a biological system [48]. Metabolomics is progressing, with powerful technology enabling the assay and detection of the huge numbers of metabolites in tissues and biofluids [49, 50]. Currently, metabolomics research can provide applicable and useful information regarding health and disease status. Metabolomics techniques such as NMR and mass spectroscopy are applied to detect and treat various cancers [49]. In recent years, the universal metabolic profiling of diseases has become feasible via the use of high-throughput analytical devices [51].

Systems approaches in cancer management

At present, researchers utilize a number of complementary omics techniques to investigate an extensive range of diseases, including cancer [52]. Major attempts have been made to apply systems biology approaches to oncology [22, 53, 54]. High-throughput and sophisticated omics technologies, such as genomics, radiogenomics, proteomics, and metabolomics, have provided a foundation for a new kind of oncological investigation [55]. These advances in experimental systems biology, along with novel analytical techniques and quantitative imaging software tools, are helping to create a more perfect image of many cancers connected to signaling routes [22, 55, 56]. Recently, metabolomics approaches have been applied as an important tool for detection, prognosis, biomarker discovery, and the design of therapeutics [57]. Denkert et al. utilized gas chromatography/time of flight mass spectrom-

Precision medicine and molecular imaging

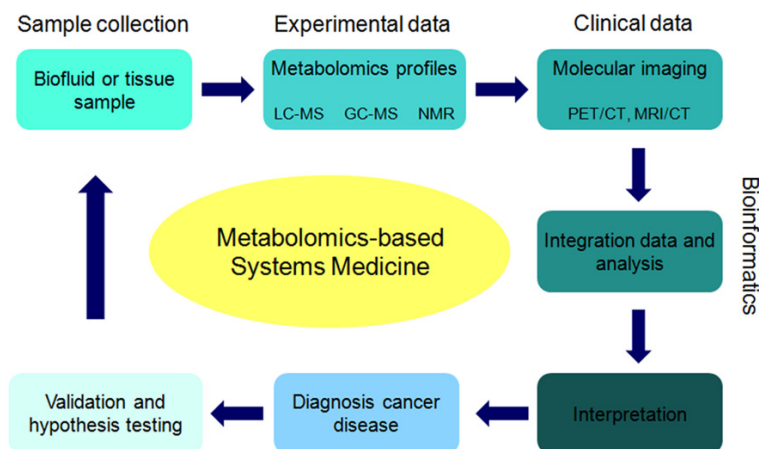


Figure 2. A schematic illustration of metabolomics-based systems medicine and molecular imaging tools into cancer diagnosis studies.

etry (GC-TOF-MS) to analyze ovarian cancer metabolism in both invasive carcinomas and borderline tumors [58, 59]. In recent studies, Japanese investigators have diagnosed gastroenterological cancer via the metabolomic discovery of a pancreatic cancer biomarker [60]. Wikoff et al. have succeeded in discovering blood-based biomarkers relevant to lung cancer screening and early detection via metabolomic analysis approaches [61]. In the field of thyroid cancer investigation, there are abundant studies demonstrating the successful application of omics technologies, such as genomics, transcriptomics, and proteomics. Metabolomics tools have been utilized in identifying a great number of metabolites in thyroid cancer in recent years [62]. Systems biology/medicine approaches also improve the understanding, treatment, and clinical management of neuroendocrine prostate cancer [63]. A schematic illustration of the metabolomics-based systems medicine and molecular imaging tools used in cancer diagnosis studies is presented in **Figure 2**.

P4 medicine

Medicine is now experiencing a major revolution that will change the current healthcare system from reactive to proactive in every way [19, 39, 64]. In fact, systems biology and the digital revolution are transforming healthcare into a proactive type of P4 medicine, meaning that it is predictive, preventive, personalized, and participatory [64, 65]. However, the term of “personalized medicine” is an expression for a revolution in medicine that will be predictive,

preventive, personalized, and participatory. This aspect of medicine was nominated P4 medicine [19, 66]. P4 medicine comprises of predictive, preventive, personalized, and participatory medicine [2, 64, 65, 67]. The essence of P4 medicine is the quantification of healthiness or wellness and the clarification of disease [68]. P4 medicine will 1) create better healthcare, 2) decrease the cost of healthcare, and 3) motivate innovation and the creation of new corporations [68]. Meanwhile, systems biology is a holistic,

universal, and integrative approach to biology. More specifically, systems medicine is a systems approach to health and disease. Systems biology provides the strategies, instruments, and computational and analytical capabilities needed to analyze huge amounts of information [19, 29, 69]. These strategies and tools can be utilized in order to combat diseases [70]. Here, we will debate precision medicine in the form of molecular imaging: 1) Personalized: P4 medicine will be ‘personalized’ because it will be established based on the genetic and epigenetic data of each person. Individualized or precision medicine may assist in data mining regarding quantitative biology and anatomy, in targeted imaging/targeted therapy, and also in the real-time monitoring of treatment response. Molecular imaging can provide special molecular profiles and assist in selecting the most efficient treatment with the minimum toxicity on a personalized basis [39, 71-73]. Imaging agents that have both diagnostic and therapeutic abilities, or ‘theragnostics’, will probably be more cost-effective and popular [39, 74]. The great advantage of molecular imaging in personalized medicine is its ability to merge physiologic and metabolic data with clinical phenotypes and provide inestimable information concerning treatments. 2) Predictive: generally, one human being differs from another by less than 1% in terms of their hereditary structure. These genetic differences cause physical differences, such as the tendency to develop various diseases [39, 75]. Medicine will be ‘predictive’ because this individual data will allow physicians to estimate the risk of particular diseases

Precision medicine and molecular imaging

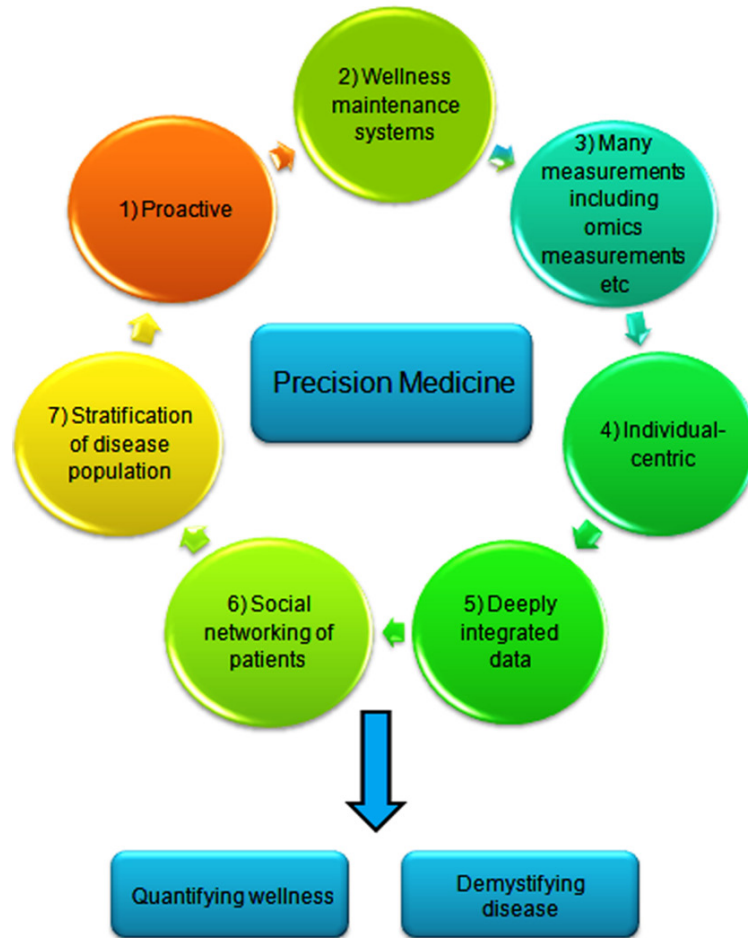


Figure 3. A schematic representation of the procedure of precision medicine (predictive, preventive, personalized and participatory) and two principal objectives of precision medicine as future of medicine comprising: 1) Quantifying wellness, 2) Demystifying disease.

in each person [39, 73]. Imaging modalities will play a meaningful role as non-invasive screening methods that are both sensitive and accurate predictors of disease [39, 76]. Investigations have shown that only PET influenced management decisions in 38% of cancer cases [39, 77]. 3) Preventive: medicine will be 'preventive' because the prediction of risk will permit the utilization of prophylactic procedures (way of life or therapeutic) to reduce this risk. Molecular/genetic screening and intervention (often directed by imaging) are the most effective methods of disease management [39, 73]. Theragnostic agents can also be used. 4) Participatory: medicine will be 'participatory' due to the fact that most of these prophylactic manipulations will require the participation of the patient. This consists of a domain of participatory activities, such data sharing, training

patients and physicians, and also counseling patients regarding individual options connected to sickness and well-being. The increasing utilization of social networks by patients, and also the activities of patients' associations, are examples of participatory actions [39, 73]. It is also anticipated that "technology singularity" and "exponential medicine", as new approaches, will shift the paradigm of medical philosophy and generate a considerable influence on the healthcare system and patient-physician relationship [78]. Here, a schematic representation of the procedure for precision medicine (predictive, preventive, personalized and participatory) and two principal objectives of the precision medicine are demonstrated (Figure 3).

Linkage of the systems approaches and precision medicine

Systems biology is growing quickly, and the term "precision medicine" has also emerged as a significant revolution in modern medicine [29, 64]. Furthermore, the biology and disease are unbelievable complicated [19, 79]. The precision medicine has extremely developed by advance of high-throughput technologies and systems approaches. Indeed, the field of precision medicine is changing the paradigm of future health care from conventional medicine practice (diagnosis and treatment) to predictive and preventative medicine and personalized health supervising [80, 81]. Progress of high-throughput technologies like high-throughput sequencing and mass spectrometry has made capable researchers, scientists and clinicians to study genomes, transcriptomes, proteomes, metabolomes, and other omics data in unexampled detail. The integrated 'omics' data can be led to a universal profiling of health and disease, and provide novel approaches for P4 medicine and health monitoring [64, 82-85].

Precision medicine and molecular imaging

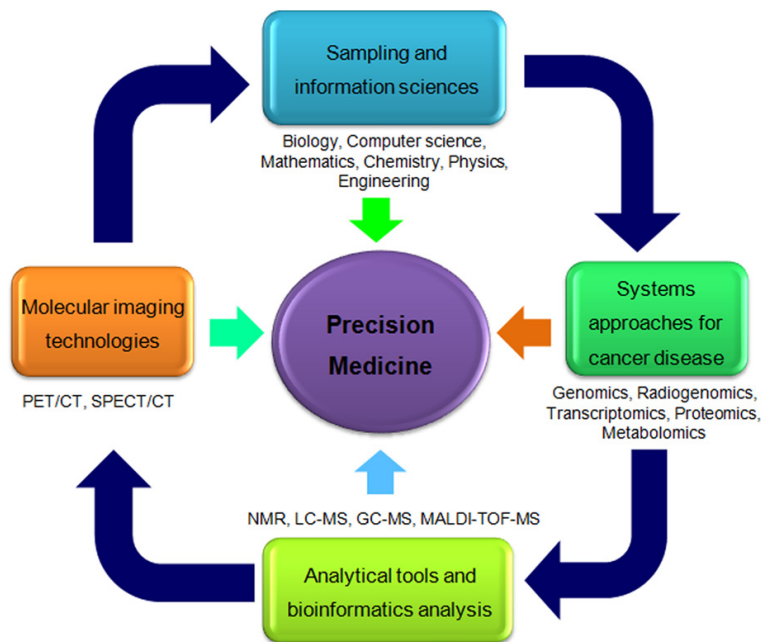


Figure 4. The components that will permit to precision medicine for discovering the biological complexity. These emerging technologies such as systems biology approaches and molecular imaging techniques will enable the implementation of precision medicine.

The power of systems biology in personalized medicine lies in disease risk estimation, personalized health monitoring and preventative medicine more significantly and it is not only for disease mechanism explanation. Systems biology provides forceful tools to supervise molecular profiles and discern delicate changes that can demonstrate network disturbance. Physicians and pathologists are energetically combining systems biology and medicine tools to attain molecular disease diagnosis [86, 87]. Regarding to undergoing period in medicine, we require contributing between systems biology and molecular imaging in the future medicine. Therefore, we will be able to estimate and monitor of personalized disease risk and health care with applying integrative omics techniques and molecular imaging technologies. We may connect systems biology and systems medicine via the implementation of omics technologies, which are the most efficient tools available in modern biology and precision medicine for disease diagnosis (**Figure 4**).

Relationship of imaging and systems approaches in precision medicine

Molecular imaging and systems biology approaches play an important role in develop-

ing precision medicine in the cancer management [88]. The evolvement of high-throughput technologies able to comprehensively evaluate DNA, RNA, protein, and metabolites in tumors management [89]. High-throughput experiments such as genomics, radiogenomics, transcriptomics, radiotranscriptomics, proteomics, radioproteomics, metabolomics and radiometabolomics provide a basis for new kinds of oncology investigation. These progresses in systems biology linked with modern analytical and also quantitative imaging software tools are assisting to create a more complete picture of many cancer related signaling pathways and personalized cancer management [22, 90, 91]. The omics technologies are major basis of systems biology.

Recently, the radiogenomics/radiomics and radiotranscriptomics technology has emerged as a new area of omics in molecular imaging field [36, 88]. In fact, novel imaging strategies in the era of precision medicine require the focus on improved characterization of disease by phenotyping disease specific imaging characteristics within the concept of genetic patient information in order to non-invasively identify patient subpopulations that benefit from similar treatments or vice versa [41]. On the other side, radiology requires “Big-Data” analysis that is feasible by bioinformatics and systems biology approaches. Since, the radiogenomics generates large amount of genotyping data by imaging from gene expression profile and genotyping variation [88]. The precision medicine requires the individual genetic data to assess many characteristics in cancer detection and diagnosis by researchers. Molecular imaging contributes with systems biology methods (such as computational and modeling) to analyze and interpret the image results. Indeed, the synergy of imaging, genomics, transcriptomics and other omics data can be constructed a bridge between systems biology approach and molecular imaging leads to precision medicine goals [36, 92-94] (**Figure 5**). These progressions provide opportunities for the

Precision medicine and molecular imaging

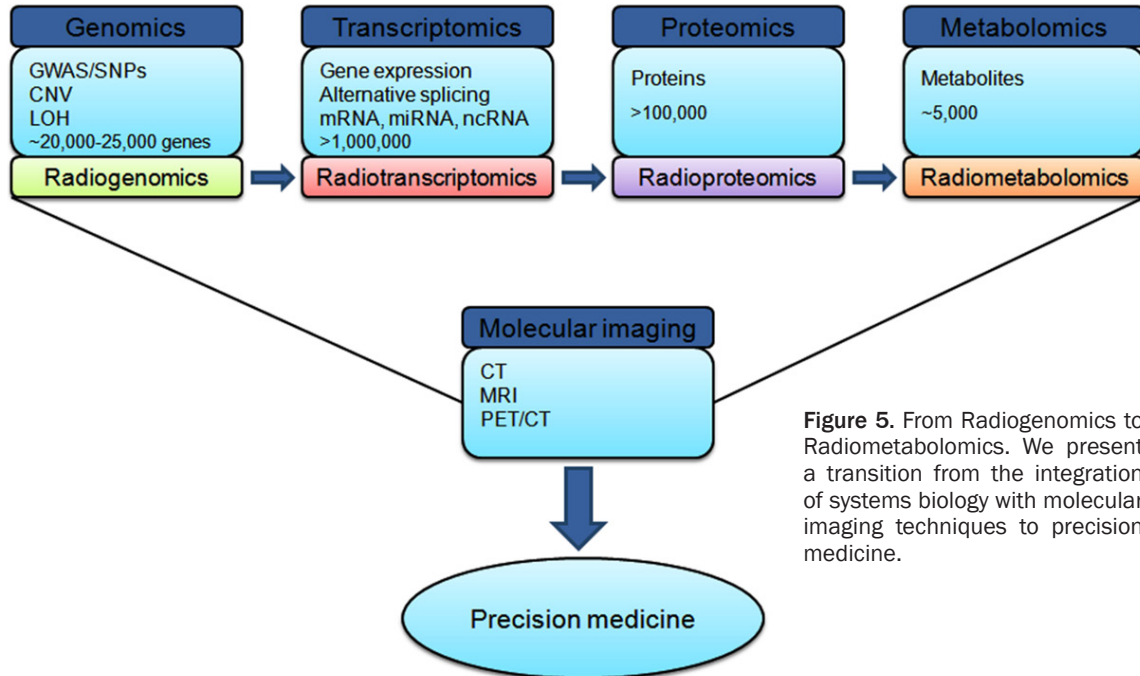


Figure 5. From Radiogenomics to Radiometabolomics. We present a transition from the integration of systems biology with molecular imaging techniques to precision medicine.

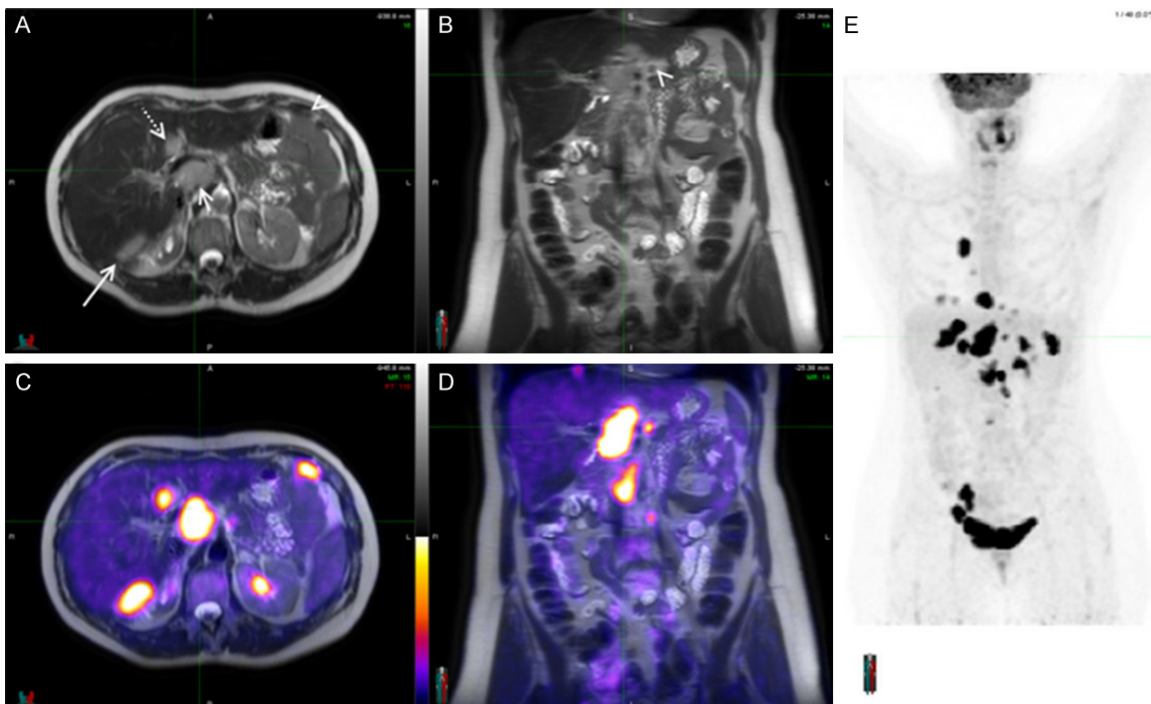


Figure 6. A typical representative of the PET/MRI imaging benefits in Precision medicine cancer care. Staging PET/MRI scan of a 56-year-old woman with ovarian cancer. The MRI images (A and B) show multiple lesions abutting the liver posteriorly (long arrow), involving the porta hepatis (short arrow) and seeding the peritoneum (arrowheads). A round, well defined lesion with same features is also visualized in segment IV of the liver (dotted arrow). On PET/MRI images (C and D) the lesions earlier described, and others not so evident, are depicted by high FDG uptake confirming their malignant nature. Maximum intensity projection of the whole body (E) reveals several lesions both in the chest and abdomen. Reproduced from [117].

advancement of personalized oncology in which cancer detection, diagnosis and therapy

are tailored to each individual's molecular profile.

Precision medicine and molecular imaging

Table 2. Comparison of emerging molecular imaging technologies for precision medicine

Imaging Modalities	Spatial Resolution	Imaging Time	Depth of Penetration	Imaging Agents and Molecular Probes	Key Utilization	
Multi-photon Microscopy	15-1000 nm	Secs	-	Fluorescent proteins, dyes, rhodamine amide, quantum dots	Visualization of cell structures	
Atomic Force Microscopy	10-20 nm	Mins	-	Intermolecular forces	Mapping cell surface	
Electron Microscopy	0.2-3 nm	Secs	-	Cyroxifation	Discerning protein structure	
Ultrasound (US)	Superficial applications Deeper applications	50 μ m, 0.01-0.1 mm 1-2 mm	Secs	mm-cm	Microbubbles, nanoparticles	Vascular imaging
CT	Preclinical Clinical	12-50 μ m, 50-200 μ m 0.5-1 mm	Mins	Limitless	Iodine	Lung and bone tumor imaging
MRI	Preclinical Clinical	4-100 μ m, 25-100 μ m ~1 mm	Mins-Hrs	Limitless	Gadolinium, dysprosium, iron oxide particles	Anatomical imaging Functional
fMRI		~1 nm	Secs-Mins	-	Oxygenated hemoglobin (HbO ₂) deoxygenated hemoglobin (Hb)	Functional imaging of brain activity
MRS		~2 nm	Secs	-	N-acetylaspartate (NAA), creatine, choline, citrate	Detection of metabolites
PET	Preclinical Clinical	1-2 mm 5-7 mm	Mins	Limitless	Fluorodeoxyglucose (FDG), ¹⁸ F, ¹¹ C, ¹⁵ O	Metabolic imaging
SPECT	Preclinical Clinical	1-2 mm 8-10 mm	Mins	Limitless	Tc-99m, In-111, I-131-labeled compounds, Ga-67, Tl-201, Peptide	Cardiovascular imaging, diagnosis of bone metastasis
Optical fluorescence imaging (OFI)		2-3 mm	Secs-Mins	< 1 cm	Peptide, integrins, matrix metallo-proteinases, caspases	characterization of cancer
Optical bioluminescence imaging (OBI)		3-5 mm	Secs-Mins	1-2 cm	Luciferins, coelenterazines, luminal, Peptide	Gene expression, cell & bacterial tracking
Surface-enhanced raman scattering (SERS) imaging		mm	Min-days	~5 mm	EGFR-SERS, EGFR affibody-gold-silica nanoparticles	Oligonucleotide targeting
Photoacoustic imaging (PAI)		~10 μ m to 1 mm	Secs-Mins	6 mm to 5 cm	EGFR Antibody-gold nanoparticles [Nle ⁴ , d-Phe ⁷]-melanocyte-stimulating hormone-gold, hormone-gold nanocages	Functional imaging of blood oxygenation
Intravital microscopy (IVM)		1 μ m	Secs-days	< 400-800 μ m, ~700 μ m	Photoproteins, fluorochromes	In development (endoscopy, skin)
Fluorescence reflectance imaging (FRI)		1 mm	Secs-Mins	< 1 cm	Photoproteins, fluorochromes	Rapid screening of molecular events in surface-based disease
Fluorescence mediated tomography (FMT)		1 mm	Mins	2-3 cm	Near Infrared, fluorochromes	Quantitative imaging of targeted or "smart" fluorochrome reporters

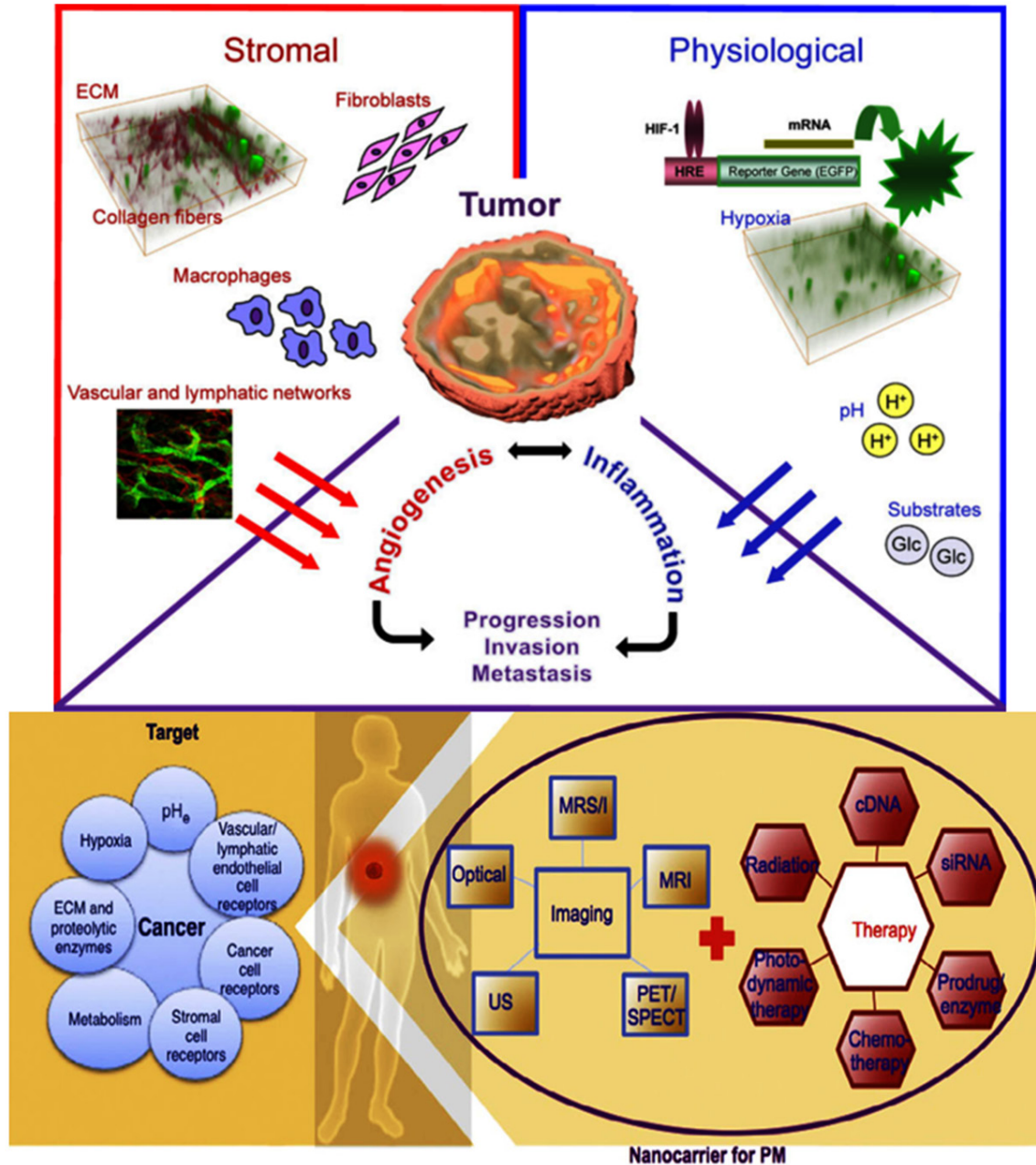


Figure 7. Schematic overview of precision medicine strategies exploiting the tumor microenvironment. Reproduced from [3] with permission of John Wiley and Sons License.

Molecular imaging technologies

In total, Imaging is an essential part in research, trials and practice in field of oncology. There has been a vast growth in the number and type of imaging technologies and their uses in past three decades, although some issues remain. At present, molecular imaging is an emerging subject that integrates advanced imaging technology with cellular and molecular biology [95].

The molecular imaging term can be defined as visual representation, characterization, measurement and quantification of biological processes at the molecular, cellular and sub-cellular within entire living organisms using specific and appropriate imaging probes [11, 96, 97]. Molecular imaging technologies play a crucial role in earlier detection, precise diagnosis of diseases like cancerous tumors, and drug development and discovery [95, 98-100]

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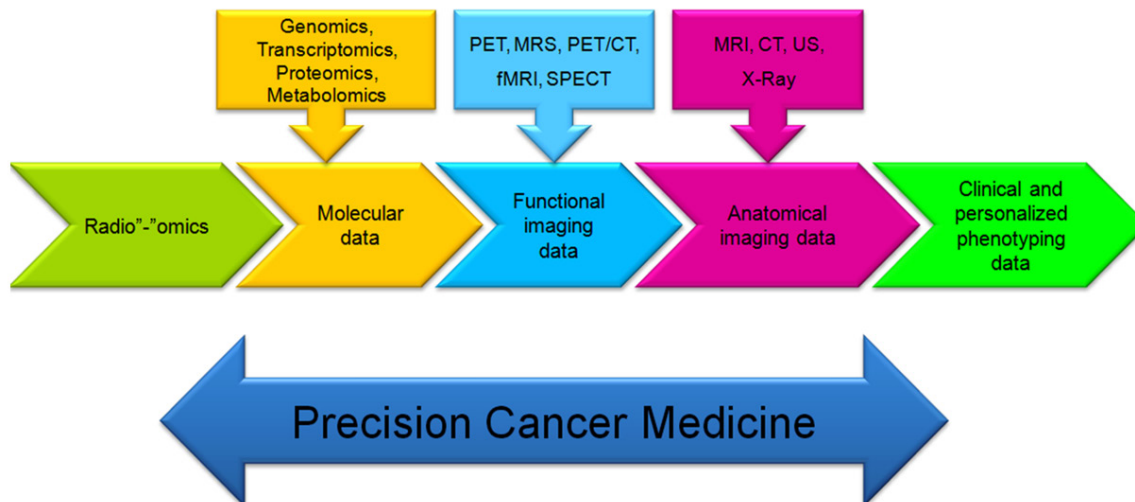


Figure 8. An overview of the integration of radio-omics, Molecular biology information and molecular imaging data in precision cancer medicine.

(**Figure 6**). Molecular imaging needs to high resolution and high sensitive tools to detect and realize specific imaging agents that connect the imaging signal with molecular occurrence [95, 101]. There are copious classes of molecular imaging agents comprising small molecules, peptides, aptamers, high-molecular-weight antibodies, engineered protein fragments, and various nanoparticles [102]. At present, only some of evolving of molecular imaging technologies is used in clinical and pre-clinical stage e.g. Positron-emission tomography (PET), single-photon-emission CT (SPECT), fluorescence reflectance imaging, fluorescence-mediated tomography (FMT), fibre-optic microscopy, optical frequency-domain imaging, bioluminescence imaging, laser-scanning confocal microscopy and multiphoton microscopy [95, 98, 102-105]. **Table 2** summarizes the characterizations and features of the some molecular imaging modalities with extraction and adaption of available references and literatures that have been published by outstanding scientists in the molecular imaging field [22, 96, 102, 105-108]. Molecular imaging modalities, imaging agents, and applications are well written by James ML and et al. [102].

Molecular imaging in cancer management

Modern molecular imaging technologies have the potential to meaningfully increase the diagnostic and therapeutic approaches for cancer treatment [109]. Molecular imaging based per-

sonalized therapy has been a fascinating concept for individualized therapeutic strategy, which is able to obtain the highest efficacy and decrease adverse effects in specific patients [5, 110-112]. Applications of molecular imaging can be assisted to detect malignant cells at cellular levels in the early stage formation of cancer [10, 113]. Molecular imaging techniques also may consider tumor characterization and cancer diagnosis without any invasive operations like biopsy or even surgery [109, 114]. Nevertheless, molecular imaging modalities and its probes are being evolved and enhanced more and more for realizing types of cancer in frame work of non-invasive procedures (**Figure 7**).

Conclusion and future perspective

Cancer is a devastating disease that modifies the metabolism of a cell and the encircling milieu. Systems biology and molecular imaging approaches are being employed to better comprehend these alterations in cancer diagnosis and therapy in the era of precision medicine. In order to successful curing of patients, early detection, precision staging and remove of cancer tissue are very important. To detect the cancer types, we require to precision medicine tools such as systems approaches (genomics, radiogenomics, transcriptomics, proteomics, and metabolomics) and molecular imaging techniques. Molecular imaging technologies have key role for enhancing cancer diagnosis

and treatment by extending imaging modalities to a functional and cellular level as well as improving intraoperative imaging of diseased and healthy tissues for surgeons. Though, medicine is now undergoing a major revolution that will change the nature of healthcare from reactive to proactive. It will increasingly transition to predictive, preventive personalized and participatory medicine (precision medicine). Meanwhile, ongoing technological progresses, particularly in the field of systems biology and molecular imaging, and also interdisciplinary cooperation with miscellaneous branches of science are compulsory for the implementation of precision medicine. These technologic improvements have been rapid in the imaging technologies such as MRI, CT, US, and imaging with radionuclides, fluoroscopy and bio-luminescence. In summary, "Radio-omics", therefore, poses as a promising contributor to the precision medicine initiative and P4 medicine, advancement both reactive and proactive measures through disease diagnosis in pre-symptomatic stages and appropriate targeting of therapeutic programs (**Figure 8**).

Acknowledgements

We gratefully acknowledge by the Persian Gulf Nuclear Medicine Research Center affiliated to Bushehr University of Medical Science, Bushehr, Iran for providing an opportunity to prepare this manuscript.

Disclosure of conflict of interest

None.

Abbreviations

BLI, bioluminescence imaging; CNV, copy number variation; CT, computed tomography; DE-NMR, Diffusion-edited-nuclear magnetic resonance; EMRs, electronic medical records; eMERGE, Electronic Medical Records and Genomics; FDA, Food and Drug Administration; FDG, 18-fluoro-deoxyglucos; FT-IR, fourier transform-infrared spectroscopy; FRI, fluorescence reflectance imaging; FMT, fluorescence mediated tomography; GC-MS, gas chromatography-mass spectrometry; GC-TOF-MS, gas chromatography time of flight-mass spectrometry; GWAS, genome-wide association studies; HPLC, high performance liquid chromatography; HPLC-MS, high performance liquid chro-

matography-mass spectrometry; iTRAQ, isobaric tag for relative and absolute quantitation; IVUS, intravascular ultrasonography; LC-MS, liquid chromatography mass spectrometry; LOH, loss of heterozygosity; MD-LCMS, Multidimensional liquid chromatography mass spectroscopy; MALDI-TOF, matrix assisted laser desorption/ionization-time of flight; MAS-NMR, magic angle spinning-nuclear magnetic resonance; mRNA, messenger RNA; miRNA, micro-RNA; MRI, magnetic resonance imaging; MRSI, magnetic resonance spectroscopic imaging; MS, mass spectrometry; NCI, National Cancer Institute; ncRNA, non-coding RNA; NIH, National Institutes of Health; NMR, nuclear magnetic resonance; OI, optical imaging; PET, positron emission tomography; RAMAN, raman spectroscopy; SERS, surface-enhanced raman scattering imaging; SNPs, Single-nucleotide polymorphisms; SPECT, single photon emission computed tomography; TEI, transthoracic echocardiography imaging; US, ultrasound.

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