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Precision medicine: In need of guidance and surveillance

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Abstract

Precision medicine, currently a hotspot in mainstream medicine, has been strongly promoted in recent years. With rapid technological development, such as next-generation sequencing, and fierce competition in molecular targeted drug exploitation, precision medicine represents an advance in science and technology; it also fulfills needs in public health care. The clinical translation and application of precision medicine - especially in the prevention and treatment of tumors - is far from satisfactory; however, the aims of precision medicine deserve approval. Thus, this medical approach is currently in its infancy; it has promising prospects, but it needs to overcome numbers of problems and deficiencies. It is expected that in addition to conventional symptoms and signs, precision medicine will define disease in terms of the underlying molecular characteristics and other environmental susceptibility factors. Those expectations should be realized by constructing a novel data network, integrating clinical data from individual patients and personal genomic background with existing research on the molecular makeup of diseases. In addition, multi-omics analysis and multi-discipline collaboration will become crucial elements in precision medicine. Precision medicine deserves strong support, and its development demands directed momentum. We propose three kinds of impetus (research, application and collaboration impetus) for such directed momentum toward promoting precision medicine and accelerating its clinical translation and application.

Key words: Precision medicine; Clinical translation; Development; Targeted therapy; Immunotherapy

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Core tip: Precision medicine aims toward accurate, efficient and effective diagnostic testing and precise treatment. Emerging techniques and therapeutic drugs based on molecular profiling and genomic characteristics will help achieve that goal. Next-generation sequencing is the most frequently used methodology for precision medicine applications; however, proteomics and metabolomics tests are growing in accuracy and ease of use. In terms of applications and outcomes, the benefits conferred by precision medicine are currently insufficient. Present development of precision medicine lacks order. Therefore, precision medicine needs strong support to develop, and a directed momentum is required. We suggest three kinds of impetus (research, application and collaboration impetus) for such directed momentum toward promoting precision medicine and accelerating its clinical translation and application.

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INTRODUCTION

Advancing technology in genomic sequencing has achieved a level of development, whereby a personal genome can now be obtained for under US\$1000 and within a day. That is approximately 3 million times cheaper and 3000 times quicker than during the period of the Human Genome Project, which ended in 2003. Toward a deeper understanding of the human genome, among both healthy and sick populations, novel disease taxonomies and new treatment options (such as basket and umbrella trials in oncological therapy) are regarded as promising areas in current medicine. Accordingly, the term "precision medicine" began appearing in the literature. A bill proposed by the United States President Barack Obama in early 2015 was expected to define disease by the underlying molecular characteristics and other environmental susceptibility factors in addition to conventional symptoms and signs.

The overarching theme of precision medicine is to classify disease more precisely, diagnose more accurately, approach treatment more individually, and undertake more specific preventions. Hitherto, almost all these aims have been based on establishing a vast data network that integrates clinical data from individual patients and personal genomic background with existing research on the molecular makeup of diseases. Based on these big data, individual treatments and customized prevention strategies have

been generated to guide clinical application, including sickness prevention, early disease diagnosis, precise therapy, and pharmacological development.

Currently, precision medicine is highly valued. Financial support has been provided through policy changes at the national level and it has received enterprise sponsorship, especially in China and the United States. However, the support has been uncoordinated. The development of the emerging discipline of precision medicine needs stronger support and proper guidance and monitoring.

PARADOXICAL STATUS QUO

Disputes and controversies have plagued precision medicine since it was first proposed. Recently, Tannock and Prasad noted the imperfect, unpromising current status of precision medicine^[1,2]. In those publications in top medical journals, the authors found that in oncology, treatment choice based on tumor molecular or personal genomic profiling confers scarce clinical benefits to patients in terms of prognosis, survival time, or quality of life. With the approach to precision medicine in recent years, several negative or inferior outcomes have appeared in numerous areas; for example, targeted therapy in oncology and imperfect application of genome sequencing in disease diagnosis. With SHIVA^[3], a randomized controlled phase 2 trial of multiple solid tumors compared the efficacy of targeted agents selected based on tumor molecular profiling (using an algorithmic approach) with that of a physician's choice. The SHIVA results showed that median progression-free survival (PFS), the primary endpoint, was almost equally poor in both cases: 2.3 and 2.0 mo, respectively. This outcome illustrates the uncertain prospects for genomic-targeted therapy in the clinical treatment of cancer.

However, the application and development of precision medicine, especially in oncology, should not be disregarded only because of certain negative results. SHIVA was based on a specific treatment-allocation algorithm, and it was unable to assess any drug's efficacy. Several aspects of that algorithm may have interpreted the PFS results as negative. Those aspects include the definition and prioritization of the specified driver molecular alterations (established in a histology-agnostic way according to the data available when SHIVA was designed in 2011). The influence of resistance aberrations and use of targeted therapies were the only options available, which rather consistently affected the identified molecular alteration directly.

There have been unpromising outcomes with some basket trials, in which molecular targeted agents were applied across diverse histologically defined tumors. However, in trials with the same single genomic alteration or some umbrella trials (in which multiple genomic alterations within the same tumor histology

were targeted), the outcomes primarily resulted from inaccuracies with current precision medicine. This in turn originated in the heterogeneity of tumors and constant evolution in the biological process of cancer^[4]. Thus, the belief that the specimen “determines” the result appears frequently in genomic research on oncology, *i.e.*, the specimen selected for a sequence determines the genome sequences of the entire tumor mass. Most current molecular targeted agents lack proper target specificity and, thus, are too short in their pesticide effect. Therefore, large datasets and molecular targeted agents with more specificity and efficacy offer much room for development.

CLINICAL DEVELOPMENT OF PRECISION MEDICINE

Prevention

Hitherto, disease prevention has emphasized etiologic treatment and early screening, which are imperfect in directionality and induce waste in manpower, material resources and funds. With the application of more accurate detection methods in the era of precision medicine, classification based on individuals with different genetic, environmental and lifestyle characteristics can be achieved. In the case of oncology prevention, subgroups with high risk factors should have a different prevention strategy from others, *e.g.*, greater frequency of health examinations or even prophylactic treatment. A large-sample study found that tumor suppressor genes in BRCA mutations may produce hereditary breast and ovarian cancer syndrome^[5]. Thus, a more rigorous prevention strategy is required for individuals carrying the BRCA mutation since they belong to the high-risk population.

Genome-wide association studies have allowed the nomination of candidate genes related to a given disease, which is helpful in identifying the disease-susceptible population^[6]. In patients with inflammatory bowel disease (IBD), over 200 genetic susceptibility loci have been identified and the gut microbiome characterized; that has promoted precise diagnosis, monitoring, and treatment of IBD^[7]. A potential contribution of precision medicine is more comprehensive, accurate understanding of morbidity and mortality trends among populations and groups with diverse cancers. Such a development is particularly pertinent to tumor monitoring and targeted prevention.

Diagnosis

Tumor molecular diagnosis has made tremendous advances following improvements in diagnostic techniques. For many years, finite genomic data have been applied to guide diagnosis, inform prognosis, and support treatment decisions with several types of cancers. For example, p53 mutations have been found to be commonly associated with microvascular

invasions, which may result in micrometastasis, followed by frequent recurrences and poor prognosis in hepatocellular carcinoma^[8].

Tumor tissue genetic sequencing has gradually become a common test in many medical centers. Circulating tumor DNA detected in the peripheral circulating blood (termed a liquid biopsy) has been validated as significant with various types of cancer; it has been especially promising in early detection, targeted agent selection, drug resistance analysis, and tumor recurrence monitoring in colorectal and lung cancer^[9,10]. Other forms of liquid biopsy (including circulating tumor cells, the exosome, and circulating nucleic acid detection) provide minimally invasive methods to diagnose and evaluate cancer status.

This progress in precise diagnosis - alone or combination with conventional examinations - has improved specificity and sensitivity in cancer diagnosis, allowing early detection. Based on divergence in multi-omics combined with conventional cancer definitions, precision medicine has the potential to achieve a new type of diagnostic categorization using unique tumor genetic profiling molecular variations, and biomarker characteristics.

Treatment

The genetic background and expression models of tumors have become clearer; it has become possible to differentiate the mutated genes in tumors from those in adjacent benign tissues. Large-scale sequencing studies have recognized genomic alterations, which are currently used to guide targeted therapy. However, another problem concerns the difficulty in identifying driver genes with gatekeeper mutation in individual genetic profiling. Driver genes have been located; however, only a small proportion of mutation genes possess specific molecular targets for drugs. Owing to the lack of proper understanding of the mechanisms of action of targeted molecular agents, targeted therapy has shown poor efficacy in many tumor patients.

Accordingly, precise classification for all cancer patients has not been achieved, and there is much room for improvement. Even so, precision medicine has heralded the dawn of oncological therapy. For example, hepatocellular carcinoma is worldwide one of the most lethal cancers, with high morbidity in South Asia. The only targeted drug for this carcinoma is sorafenib, which was approved by the United States Food and Drug Administration. Following dedicated genomic profiling in recent years, several targeted drugs, such as regorafenib^[11] and lenvatinib^[12], have been identified and verified. Those drugs will be used instead of sorafenib and improve the therapeutic efficacy in patients with advanced hepatocellular carcinoma.

Treatment will become more precise and effective through proper, beneficial screening of patients, rather than adopting a unified therapeutic strategy for

patients with the same cancer. This may be achieved by genome sequencing to identify therapeutic targets and more reliable molecular classification of a tumor, as well as broadening the utility of existing molecular targeted drugs in precision oncology.

One of the main goals of precision medicine is maximizing the therapeutic effect and minimizing the occurrence of adverse drug reactions by identifying the correct agent and dose for each patient. Numerous advances in precision medicine have been made in determining and understanding how such factors as genetic polymorphisms influence drug pharmacokinetics (PKs) and contribute to variable drug responses (VDRs). For example, alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD), the most common chronic liver diseases in Western society, have been demonstrated to possess a close relationship with intestinal microbiota compositions. Studies have described how products secreted by microbiota-derived metabolites could influence the PKs and VDRs of drugs used for treating ALD and NAFLD^[13]. With deeper understanding of host-microbial interactions, novel therapeutic methods targeted at gut microbiota could enable new treatment options to restore the intestinal ecosystem and cure liver disease.

THREE KINDS OF IMPETUS TOWARD DIRECTED MOMENTUM

Precision medicine is currently weak; that has restricted its clinical application and popularity. Negative outcomes in personalized therapy based on individual molecular profiling have also been discouraging for precision medicine. However, the objective pursued by precision medicine deserves approval, and a collaborative impetus is necessary to promote it. Precision medicine pursues its aim based on genetic, biomarker, phenotypic and psychosocial characteristics toward a therapy that targets the needs of individual patients; it distinguishes one patient from other patients with similar clinical presentations. Achieving precision medicine requires a directed momentum. Impetus from diverse aspects should be emphasized as follows.

Research impetus

The orthocenter of precision medicine should not be situated merely in oncological research; it should expand to other disease categories, such as contagious and rare diseases, chronic illnesses, and even among healthy populations. Studies in precision medicine must establish a foundation to construct a reliable biological information database, including proteomics, metabolomics, genomics, epigenomics, and even mobile health technology, that underpins all humanity. Such a development needs a broad research plan to encourage creative approaches to precision medicine.

However, multiple issues hamper this process; they include reluctance to collaborate among professional societies, clinicians and reimbursement organizations. There is a lack of robust criteria to accommodate strict requests for prospective controlled clinical trials, aiming to verify the superiority of an individualized approach for drug prescription based on personal molecular profiling. There is likewise a lack of a reliable reference method for comparing a patient's genome with the greater population's "normal" genome.

Thus, research has emphasized empowering clinicians, patients and investigators to work together toward more personalized care, improving clinical outcomes, and establishing an effective patient cohort, wherein both clinical and multi-omics^[14] data are collected.

Application impetus

The clinical application of precision medicine is not limited to molecular targeted therapy and personal genomic sequencing. Precision medicine possesses broader connotations, which include omics analysis, molecular detection, biomarker promotion, molecular imaging, and molecular pathology. Those areas depend on further advances in medical informatics and bioinformatics. Precision medicine will work effectively when the medical establishment integrates research to provide evidence for constant, iterative improvement of medical practice in different disciplines.

Personalized treatments and methodology in precision medicine can also complement conventional therapy and novel immunotherapy, such as immune checkpoint inhibitors in cancer treatment enhancing the clinical benefits. Using whole-exome sequencing, Le *et al.*^[15] revealed that colorectal cancers with amounts of somatic mutations induced by mismatch repair defects are more susceptible to immune checkpoint blockade with pembrolizumab (a PD-1 antibody). Van Allen *et al.*^[16] analyzed whole exomes from 110 patients with metastatic melanoma; they found that overall mutational load, neoantigen load, and expression of cytolytic markers in the immune microenvironment were highly correlated to the response of CTLA-4 inhibitor.

Following genomic detection in a population showing inconsistent responses to the same chemotherapeutic agents, molecular profiling has been confirmed to be related to chemotherapy sensitivity. Although this correlation is not strong enough to inform drug selection in all diseases, personalized therapy has been successfully achieved in some patients. Applying the methodology of precision medicine based on traditional therapy and immunotherapy may therefore help uncover discrepancies in populations and locate the sources of different curative effects. These discoveries could translate to enhancers or reinforcing agents overcoming inefficiency and resistance with existing therapies.

Collaboration impetus

The development of precision oncology does not involve repudiation of evidence-based medicine. Almost all present clinical applications of precision medicine refer to evidence-based medicine. To explore the real effects of applying precision medicine to the individual, precise medical practice and validation need to be combined with methodology analogous to real-world research^[17].

In the era of precision medicine, robust and thorough supervision should be implemented - especially in commercial genomic sequencing and individual genome consulting. To make the market more canonical and accelerate the merging of precision medicine with evidence-based medicine, related administrations and organizations need to devise detection standards and industry norms. Governments should be responsible for formulating policies that ensure the sound development of precision medicine, leading to virtuous competition, accelerated clinical translation, and providing sufficient freedom to promote cooperation among courses. To maximize the benefits of precision medicine, pharmaceutical companies should undertake more clinical trials and drug development for treating infrequent cancers, such as cholangiocellular and vascular endothelial carcinoma.

CONCLUSION

There is a significant gap between precision medicine and its application in clinical settings and for disease prevention. However, precision medicine is not illusory for medical development; its essence is exploring novel technology to assist with acute interventions in individual patients by generating and using numerous sources of personal data to group and treat patients more accurately. Pursuing precision medicine demands directed momentum based on the impetus from research, application, and collaboration. All players and aspects - academic, social, policy, and economic - should coordinate toward promoting precision medicine.

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