Review

Clinical Implementation of Precision Medicine: Current Challenges and Future Perspectives

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Precision medicine has attracted tremendous global attentions in the past few years. A great deal of strikingly successful cases using targeted therapies for cancers and other critical human diseases have been reported and proved the effectiveness of genome-based personalized treatments. The emerging technologies of next generation sequencing (NGS) enable us to decode genetic alterations in a high throughput mode and detect all potential pathogenic mutations simultaneously. Although precision treatments have shown promising perspectives, adoption of precision medicine in clinical settings remains far from satisfactory, especially in the underdeveloped regions. The major challenges include: 1) yet to be standardized genetic tests; 2) Delayed targeted drug development; 3) high cost of targeted drugs; 4) slow acceptance by clinicians. In this review, we will discuss these main obstacles for advancing the precision medicine, and provide insights on how global efforts may need to work out a strategic plan to accelerate the precision medicine and improve the quality of human health.

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INTRODUCTION

Targeted cancer therapies are drugs or substances that block the growth and spread of cancer by interfering with specific molecular targets that are involved in the growth, progression, and spread of cancer.[1] It is now referred as precision medicine. Precision medicine has evolved from early concepts such as from-bench-to-bedside,[2] translational medicine,[2] targeted therapy,[3] and personalized medicine.[4] The basic idea of precision medicine is to provide optimal treatments by matching precise targets through molecular diagnosis. Compare to targeted therapies, which drugs exert its effects primarily on abnormal cells, chemotherapy affects all divisible cells. Therefore, chemotherapy can be more toxic and cause severe side effects.[5-6] The rapid development of precision medicine has shed lights on curing critical human diseases such as cancers. Genome-based personalized treatments for cancer have achieved great success in the last decade.[7-10] Next generation sequencing (NGS) technology makes precise detection of all potential pathogenic mutations simultaneously possible. Although precision treatments have shown promising perspectives, the adoption of precision medicine by clinicians remains challenging, especially in the underdeveloped regions. In this review, we will discuss some major obstacles and provide insights into potential solutions to the issues.

GENETIC TESTING NEEDS TO BE STANDARDIZED

The very first step of precision medicine is to accurately identify drug targets so that potential drugs may be matched for personalized treatments. Single gene mutation(s) may be detected by PCR or real-time PCR (ARMs) techniques.[11] Multiple gene mutations have to be done by high throughput methods such as NGS.[12] Hotspot cancer gene panels include well studied driver mutation genes that cause progress of majority cancers, normally having corresponding target drugs.[13] Whole exome sequencing covers all 21 thousands protein coding human genes that allows finding of *de novo* gene mutations and copy number variations.[14] Whole genome sequencing can provide complete genomic features also include chromosomal structure variations such as translation, inversion, large indels, and duplications, which other sequencing approaches cannot offer.[15] In the US, there are more than 2000 genetic testing firms that have been established in the last 5 years.[16] Genetic tests have been used in clinics for many inherited diseases with single point mutation,[17] but its application to complex diseases with multiple genes/mutations such as cancers is yet to be standardized and regulated. Take lung cancer as example,

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there are many testing options that can be selected such as EGFR and KRAS gene mutations,[18] cMET gene amplification,[19] ALK-EML4 and ROS1 gene fusions,[20] PD-L1 immunohistochemistry,[21] 48 or 45 hotspot cancer gene panels,[13] whole exome sequencing,[14] and whole genome sequencing.[15] What genetic test or combinations are the most appropriate for an individual patient? Different types of cancers need customized genetics tests based on its anatomic pathology diagnosis. Before a genetic test is chosen, we must know the characteristics of the lung cancer. For example, is it an adenocarcinoma or squamous carcinoma? In very competitive genetic testing markets, the cost of testing may become a key factor. However, simply choosing a single gene test for the sake of its lower cost may exclude the possibilities of matching certain targeted drugs. On the other hand, it is not feasible to perform whole genome/exome sequencing for all patients due to its high cost and no access to medical insurance. In case of clinical research, it may be helpful to obtain more genetic information for rare diseases with unknown target, whole genome/exome sequencing is a powerful technique for *de novo* gene mutation identification. For example, recently our lab sequenced the tissue sample from a patient with olfactory neoblastoma, a very rare malignant tumor. We identified a few *de novo* mutations that matched with existing targeted drugs approved for other cancer treatment. The patient showed complete response after one-month treatment.[22] Most importantly, the quality and accuracy of genetic test must not be compromised in the competitive field. Therefore, standardized and regulated protocols and guideline are mandatory in clinical genetic test laboratories to warrant the balance and correct clinical practice for precision medicine.

Table 1. Common Molecular targets of FDA-approved drugs

Targets	Target Drugs
ABL1	Bosutinib, Dasatinib, Imatinib, Nilotinib, Sorafenib, Vandetinib
ABL2	Dasatinib, Nilotinib
ALK	Ceritinib, Crizotinib
BRAF	Dabrafenib, Regorafenib, Sorafenib,Vemurafenib,
CSF1R	Sunitinib
EGFR	Afatinib, Cetuximab, Erlotinib, Gefitinib, Lapatinib, Panitumumab Vandetanib
EPHA2	Dasatinib
ERBB2	Afatinib, Emtansine, Lapatinib, Pertuzuma,Trastuzumab
FGFR1	Pazopanib, Regorafenib, Sorafenib, Sunitinib
FGFR2	Pazopanib, Regorafenib, Sorafenib, Sunitinib
FGFR3	Pazopanib, Sorafenib, Sunitinib
FLT3	Cabozantinib, Pazopanib, Regorafenib, Sorafenib, Sunitinib, Vandetinib
JAK1/2/3	Ruxolitinib
KIT	Axitinib, Cabozantinib, Dasatinib, Imatinib, Nilotinib, Pozapanib, Regorafenib Sorafenib, Sunitinib
MEK	Trametinib
MET	Cabozantinib, Crizotinib
MTOR	Everolimus, Sirolimus,Temsirolimus
PDGFRA	Axitinib, Dasatinib, Imatinib, Nilotinib, Pozapanib, Sorafenib, Sunitinib
PDGFRB	Axitinib, Cabozantinib, Dasatinib, Imatinib, Nilotinib, Pozapanib, Ponatinib Regorafenib, Sunitinib
RAF1	Regorafenib, Sorafenib
RET	Cabozantinib, Pazopanib, Regorafenib, Sorafenib, Sunitinib, Vandetinib
SRC	Bosutinib, Dasatinib
TEK	Pazopanib
TIE2	Cabozantinib
VEGFR1/2	Axitinib, Bevacizumab, Cabozantinib, Pazopanib, Regorafenib, Sorafenib Sunitinib,Vandetanib,
VEGFR3	Axitinib, Cabozantinib, Pazopanib, Sorafenib, Sunitinib,Vandetanib,

NEW TARGET DRUG DEVELOPMENT IS BEHIND THE DEMAND

Currently, there are more than 100 targeted drugs have been approved (**Table 1**) and 600 others in different stage of development for cancer treatments.[23-24] Imatinib was one of the very first success tyrosine kinase inhibitors (TKIs) targeting the EGFR mutations for treatment of non-small cell lung cancer (NSCL).[25] Besides small molecule drugs, there are also biologic drugs such as bevacizumab, which targets to VEGF, have been added to the family of targeted medicines.[26] Most recently, anti-immunologic targeted drugs such as Keytruda and Opdivo have been approved by FDA for various malignant tumors.[27-28] These anti-PD-1 drugs show striking anti-tumor effects, and pave the way for anti-cancer immunological therapies. Despite of the ongoing efforts on development of new targeted drugs, the demand of novel drugs has far outpaced the new drug development. The emerging next generation sequencing (NGS) technologies allow us to discover large scale *de novo* genome alterations and new drug targets. The frequency of a given driver gene mutation is low in solid tumors,[29] thus, a targeted drug is normally effective only to small portion of same type of cancers. For example, only 3 percent of patients with lung cancers carry cMET amplifications that may be responsible to crizotinib treatment.[19] The increasing cap between *de novo* gene mutations and unavailable targeted drug often causes awkward

situation for clinicians to refer genetic testing to the patients, where in many cases there was no targeted therapy available to the identified gene mutations. One possible solution is to conduct large scale genome-base clinical trials to validate the off-label drugs, the other is for pharmaceuticals to develop multi targets drugs or single target drugs for multiple cancers. In fact, currently more than 2000 genome-based clinical trials are conducted in the USA,[16] and many drug makers are developing new drugs that could be potentially used cross multiple cancers.[30] Regional FDA regulatory restrictions for newly marketed drug approvals further slowdown the global access of target therapies. For instance, currently more than 100 targeted drugs for cancers have been approved by FDA worldwide, however, only about 40 of those marketed drugs were approved by the Chinese FDA to be used in China today.[31] Therefore, global collaborative efforts need to be established for fast track marketed drug approvals.

HIGH COST OF TARGETED DRUGS PREVENTS ITS USAGE

The cost of targeted drugs is another obstacle for widespread clinical implementation of precision medicine. Most of the current patent-protected targeted therapies are extremely expensive and not covered by medical insurance worldwide. For example, the monthly cost for Keytruda, a PD-1 drug, is over 5000 US dollars.[32] Majority cancer patients are not able to afford such high cost. While a few generic targeted drugs that are manufactured from third party countries are available at lower cost to the underdeveloped regions, it is not sufficient to change the frustrated situations that patients are not able to pay the expensive drugs even though their genetic testing results matched certain targeted drugs. Several drug makers have set up promotion programs to offer free accessible targeted drugs after patients took certain cycles, others provide discounted prices for patients to subscribe. Recently the Chinese government has covered about 67 percent of certain targeted drugs including Gefitinib and Imatinib for its medicare program.[33] Some regions also partially cover the genetic testing to patients who are eligible for targeted therapies, however, this tiny move does not solve the highly demanding of targeted drugs from the low income communities. To solve the problems, global efforts, particularly from drug makers, world health organization and local governments, will be needed to further cut down the cost the target therapies.

CLINICAL GUIDANCE AND EDUCATION FOR ONCOLOGISTS ARE CLEARLY NEEDED

Beside the roadblocks of genetic testing, deferred target drug development, and cost for available drugs described in the early sections, definitive clinical guidance and systemic training on precision medicine to oncologists are absolutely needed. Currently, surgery followed by chemotherapy and radiation therapy remain the major treatment protocols as traditional cancer therapies.[22] Only those individuals at very late stage of cancers who failed to chemotherapies/radiation and not suitable for surgery may be recommended to targeted therapies.[34] Some clinicians are reluctant to adopt the precision medicine approach due to the lack of appropriate genetics knowledge and targeted therapies as needed. Furthermore, clinicians from community hospitals and even second tier healthcare settings, may not be aware of precision medicine at all. Thus, patients who see doctors in those settings may completely lose the treatment opportunities to targeted therapies. To remedy the situations, the NCCN and ACMG guidelines need frequent updates with emerging targeted drugs and genetics testing protocols. Training and educational programs in precision medicine may be needed for oncologists from all tiers healthcare. Patients should also be able to access educational resources to understand the advantages and disadvantages of precision medicine comparing to other therapies.

CONCLUSION AND FUTURE DIRECTIONS

Current pace of targeted drug development is far behind the high demand of more effective drugs for target therapies. Oncologists without appropriate genetics result interpretation and target therapy training are reluctant to get involved in the clinical practice of precision medicine.

Currently genetics testing and target therapies are performed in separate settings. Genetic testing party only focused on test report but does not assume responsibilities for therapy recommendations. In the future, we suggest to implement an integrative program in healthcare setting for genetic testing and results interpretation, targeted therapy recommendation and continuous monitoring of therapeutic responses from the recommended treatment regimen to warrant effective operation of precision medicine. Expensive target drugs and difficult accessibility to majority cancer patients, especially to the individuals from the underdeveloped regions make the real world clinical implementation of precision medicine even more challenging. Global collaborative efforts among drug makers, world health organizations and regional governments are necessary to address the unmet need to accelerate the clinical implementation of precision medicine.

CONFLICT OF INTEREST
None.

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