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Drug Sensitivity Tests for Personalized Cancer Therapy

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Personalized cancer therapy is defined as the tailoring of therapies according to the genetic profile and molecular background of individual patients. Therapeutic strategy is designed based on empirical and bioinformatics analysis of each individual cancer sample. Personalized cancer therapy is proposed to be the future of cancer treatment that can provide patients with maximal treatment efficiency and less toxicity.

In the past, cancer treatment is administered to patients solely based on the origin and stage of cancer. However, researchers and doctors gradually realized that the same treatment that suits one patient might have a different outcome when treating another patient with the same cancer. In the late 1940s, Jane Cooke Wright, M.D., started to explore the tailoring of cancer treatment by correlating the *in vitro* and *in vivo* response of her patients' cancer biopsy [1]. Nevertheless, limited progress was achieved due to limited technology, insufficient research and legislation issues on human subjects. The $215 million Precision Medicine Initiative® announced by former US president Barack Obama in his 2015 State of the Union address [2] promoted research and accelerated clinical drug approval. On one hand, the US Food and Drug Administration (FDA) have accelerated approval for drugs in targeted therapy and immunotherapy that have significant anti-cancer effect [3]. On the other hand, the US FDA rapidly approved clinical diagnostic tests including genetic tests [4], circulating tumor cell (CTC) harvesting kits [5,6], *etc.* which greatly improved personalization of cancer therapy *in clinico*. On the global scale, many countries have initiated funding programs towards personalized cancer therapy including China, the UK, and many countries in Europe.

Broadening of diagnostic and therapeutic spectra provided clinical doctors with more options (Table1). However, guidelines on making therapeutic decisions lagged behind. Unlike targeted therapy that has very specific biomarkers to trace, the outcomes of many treatment options could hardly be predicted before treatment. Hence, evidence-based drug sensitivity tests emerged to address this issue.

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Table1: Examples of common cancer therapies

Therapy type	Example	FDA approved cancer type(s)	Pros and cons
Surgery	Mastectomy	Breast cancer.	Pros: Physical removal of cancerous tissue. Cons: Incomplete removal increases risk of relapse.
Chemotherapy	Cisplatin	Metastatic ovarian cancer; metastatic testicular cancer; bladder cancer.	Pros: Effective in mostcases. Cons: Developmentof resistanceafter prolonged treatment; substantial side effects e.g. nephrotoxicity, ototoxicity, myelosuppression, *etc*.
Radiotherapy	External Beam Radiation Therapy (EBT)	Breast cancer; lung cancer; colorectal cancer; esophageal cancer.	Pros: Localized treatment; no need formastectomy. Cons: Radiation toxicity.
Targeted therapy	Trastuzumab (Herceptin®)	Breast cancer; metastatic gastric or gastroesophageal (GE) junction adenocarcinoma.	Pros: Specific for HER2+ breast cancer. Cons: Side effects e.g. cardiomyopathy, pulmonary toxicity, neutropenia.
Hormone therapy	Tamoxifen	Breast cancer.	Pros: Effective for estrogen receptor (ER) positive breast cancer. Cons: Limited application.
Immunotherapy	CAR-T cell therapy	Acute lymphoblastic leukemia (ALL).	Pros: Engineered T cells that specifically target on cancer cells; Personalized treatment. Cons: Concerns about cell therapies; certain gene mutations may compromise treatment [7, 8]; limited application.

Chemotherapy: a double-edged sword

Among all types of cancer treatment methods, chemotherapy remains the most prevalent method due to its feasibility in most cancers and affordable cost. However, chemotherapy has diverse response in different cancer patients and strong side effects. Hence, drug sensitivity test to screen for effective chemotherapy drugs with low toxicity will optimize decision-making.

In order to carry out drug sensitivity tests, biopsy is usually carried out to retrieve primary cancerous tissues from patients. Liquid biopsy enables harvesting of large quantities of cancer cells in blood-borne cancers that can be directly used for drug screening. CTC extraction from liquid biopsy followed by *in vitro* amplification is vastly tested, but efficacy is mainly achieved in late-stage cancers. Needle biopsy on solid tumors followed by *in vitro* tumor amplification is applicable to early-stage cancers, but is limited to superficial tumors.

Tumor amplification can be done by patient derived xenograft (PDX) models, two-dimensional (2D) monolayer cell culture and three-dimensional (3D) organoid culture. While PDX model is considered as a relevant *in vivo* model [9], the time consumption of more than 2-4 months [9, 10], low screening throughput and cost of model establishment remains the biggest concern for real-life applications. Some researchers thus proposed the use of PDX-derived cell lines as complementation for mouse models to perform high throughput drug screening. In parallel, humanized mouse models have been adapted to optimize tumor microenvironment. Alternatively, *in vitro* models have been developed for high throughput drug screening to circumvent the drawbacks of xenograft models. 2D monolayer cultured cell lines are derived from primary tumors [11] due to its capability to grow rapidly *in vitro*. However, monolayer cultured cells are considered less relevant nowadays with our enhanced knowledge of tumor microenvironment. In light of this, National Cancer Institute (NCI) announced abolishment of using NCI-60 cancer cell lines for future drug screening tests [12]. 3D organoid culture was first developed in 1950s [13, 14], but did not gain attention in drug screening until recent years [15, 16]. The mimicry of 3D environment in organoid cultures is its major virtue, and proves it to be more closely representative of its primary tumor. Furthermore, researchers are also trying to optimize tumor microenvironment in organoid cultures by adding stromal cells and blood vessel-mimicking modules by architectural engineering of culture devices [17, 18]. However, these methods are still at its infant stage and cannot replace *in vivo* models up to date.

In contrast to tumor amplification, reducing sample requirement for high-throughput drug screening

by application of microfluidic devices is an alternative approach. These methods mainly compensate for the long amplification time and limited sample quantity. For instance, a novel droplet microfluidics technique was adapted to screen multiple treatment conditions in parallel using human primary tumor dissociated cells suspended in nano-liter droplets with a rapid turnover between 16-24 hours [19]. Nevertheless, resuspended cancer cells lack the diversity of microenvironment. In order to assess the propensity of whole tissue response, insertional microfluidic device was developed for *in situ* drug screening by Jonas, *et al* [20]. Nevertheless, tissue screening had limited throughput and are barely feasible on tiny early- stage cancer samples.

Conclusion and insight

Although drug sensitivity tests were shown to provide insight to clinical decision, more research is needed to prove that any of the methods are reliable *in clinico*. A major hurdle is legal regulation on clinical trials. For countries where off-label drug administration is legal, the risk of medical liability deters many clinical doctors to try adopting treatment options suggested by drug sensitivity tests. Notwithstanding, collaboration between research institutes and hospitals is gaining momentum after government-initiated movements were engaged. In addition to efforts on fostering genetic sequencing and drug sensitivity tests, advancement in gene editing techniques like the CRISPR/Cas9 system [21] could greatly enhance the establishment of *in vivo* models for disease analysis. Immune hijacking by training the patients' own immune cells (CAR-T) provides an alternative route in personalized cancer therapy. However, application and limitation of immunotherapy remained elusive. Preliminary studies on combining meta-analysis of relevant medical records including treatment regimens and outcome in correlation to genetic tests, histopathology results, *etc*, have also been initiated in various countries. Nevertheless, the comprehensiveness and accuracy of medical recording systems typically varies, hence cautions on the interpretation of these data.

In conclusion, although drug sensitivity tests provide evidence-based insight for therapeutic decision-making, the combination of other analytic methods is critical. More research is needed to improve each method, and more relaxed legal regulation regarding clinical trials might promote these pursuits.

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