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Review Article

# Individualized Cancer Therapy, what is the Next Generation?

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## Abstract

Cancer is the secondary most frequent cause of disease-induced human mortality worldwide. Yet, it is different disease with a universal feature of unlimited growth, sometimes invasive and remote metastasis (> 100 different pathogenic types). Individualized cancer therapies/personalized cancer therapies (ICT/PCT) are targeted to cope with the tricky character of disease diversity. The next generation of ICT/PCT must simultaneously contain information of pharmacology (drug sensitivity), oncology (tumor etiology/pathological information), computational network and patient's desire (decision-aid). Any unilateral efforts could not be able to reach maximum beneficial outcomes in clinics. This future trend is inevitable. In addition, anticancer drug combination might undergo great changes and optimum. After all, integrated clinical ICT/PCT systems (collective personalized paradigms) might make a difference for cancer treatments in future.

***Keywords:*** *Individualized Cancer Therapy; Personalized Medicine; Pharmacology, Neoplasm Pathology, Drug Combinations; Neoplasm Metastasis; Decision Aid*

## Backgrounds

Cancer as the secondary most frequent cause of disease-induced mortality causes annual human mortality of 7 - 10 million worldwide [1,2]. As cancer is a different disease, the hallmarks of cancer pathogenic traits vary in tumor genomic mutation/translocation/abnormality and with tissue origin/disease stages in the clinic [3,4]. Several types of individualized cancer therapy/personalized cancer therapy (ICT/PCT) have been designed for choosing anticancer drugs in the clinic [5-10] - include drug sensitivity test (DST) [11-13], tumor biomarkers/bioinformatics detection [14-18], pharmacogenetics (PG) [19-21], individualized antimetastatic therapy [22,23], drug combinations [24], cancer assistant therapy [25,26], patient's decision aids [27,28] and so on [29-31]. Some of them, such as DST have been established over 60 years.

### Major characters of current ICT/PCT disciplinary

#### Therapeutic benefits vs survival benefits by DST utility in the clinic

From the surface, drug responses (partial response-PR or complete response-CR) in cancer patients are improved by DST utility. However, only less than 25 - 30% clinical therapeutic data state a survival benefits by current ICT/PCT. In most cases, patients' survival is almost the same in spite of DST or other ICT/PCT discipline utilities [11-13]. In addition, these kinds of survival elongations are only several weeks/months that is far beyond our requirement-long term disease-free for late-stage of cancer patients.

## Biomarkers and bioinformatics

Bioinformatics is a modern approach that provides by a variety of techniques (omics) for mining and analyzing overall tumor abnormalities of DNA, RNA, proteins and glycoligands in human bodies [14-18]. Presently, the best example of utilizing cancer biomarkers or bioinformatics is for revealing abnormal proteins of cancer antigens. Though previous practice has established workable routines (more than 10 biomarkers) in general hospitals, it is not perfect for drug choice.

Why do we give this conclusion? If we know all information of tumor origin and pathological progresses, we still cannot determine which type of anticancer drug is most suitable. Anticancer drug activity is not parallel with oncology in mathematical ways. The pharmacological data of drug is more complicated comparing with mathematical/physics data analysis of oncologic changes.

## Pharmacogenetics (PG) for cancer therapy

By entering this millennium, clinical applications of PG have been greatly intensified worldwide, especially PG for hepatic or other organ metabolism enzymes in human bodies. Presently, the purpose of PG anticancer study is mostly to predict the fraction of active or inactive metabolites. The final required dosage of a drug is deduced from the genetic variation of metabolic enzymes in tumors or human bodies [19-21] (Figure 1). Overall, PG study at this stage is an effort to maximize efficacy and minimize toxicity of drugs in individual patients. Yet, present PG can only detect a narrow-range of human genes and improperly judgment of anticancer activity of drugs in most patients.

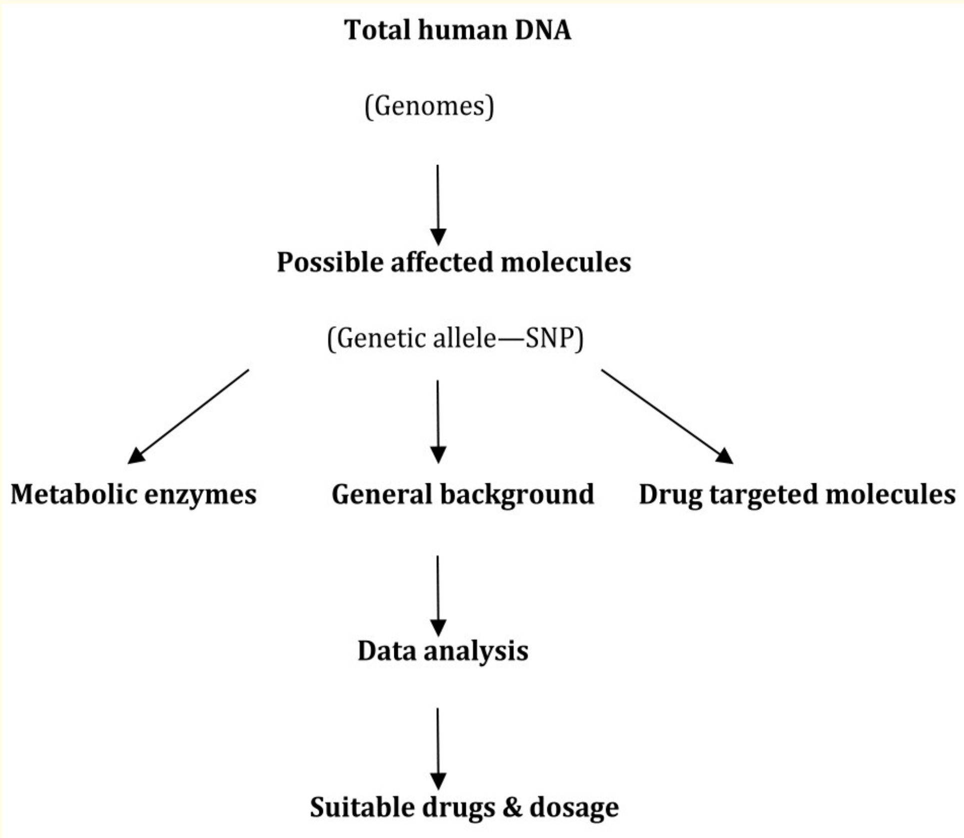


***Figure 1:*** *The schematic diagrams of cancer therapeutic PG.*

### Individualized antimetastatic chemotherapy

Similarly, large portion of cancer mortality (90%) is caused by cancer metastasis [32-35]. However, DST commonly evaluates drug response to primary tumor. No specific therapy against metastatic tumors fails for improving patients' survival. This shortcoming will greatly undermine current ICT/PCT imperfection.

Since cancer metastasis plays key role for cancer deaths, it is reasonable to garner growing attentions of neoplasm metastasis from individual patients. Individualized antimetastatic chemotherapy is to treat cancer according to different stages of neoplasm metastasis [22,23].

However, until now, clinical cancer treatments are mainly focused on primary tumors. Antimetastatic drugs are not widely developed [36-43]. Due to this knowledge deficiency, any small breakthrough for antimetastatic therapy is supposed to make a great difference in cancer therapies. Apart from this antimetastatic drug development, antimetastatic drug targets [44-61], especially against formed metastatic foci are top priorities in cancer treatment study. Some new PCT/ICT modality with this function can be valuable avenues for this breakthrough.

Therapeutic dilemma in metastatic treatment has been noticed. More recently, it is known that transmission of primary tumor into mobile status (floating in the vessels) is the transmission from epithelial to mesenchymal (EMT) and transmission of mobile tumors to metastatic nodules in remote organs is from mesenchymal to epithelial (MET) [62-66]. Thus, it might be mechanistically therapeutic oppositions between primary tumor and formed metastatic tumors.

**Primary tumors → EMT → Circulating tumors → MET → Metastatic nodules**

***Figure 2:*** *Overall picture of pathological mechanisms from primary tumors and metastatic tumors [74].*

There is an opposite biological pathways and mechanisms between primary tumor and metastatic tumors. So, it is proposed that anticancer agents inhibiting primary tumors might be a promoter to metastatic tissues [67,68]. Facing this therapeutic dilemma, we argue that drug combinations/biotherapy may be helpful for this clinical situation [68-71].

### Drug combinations

Most cancers have multiple genetic alterations and molecular abnormalities, especially for late-stage cancer patients. Drug combination might help us on this matter [72,73]. Generally speaking, anticancer drug cocktail might be one of the good solutions for cancer therapy [74-78]. However, it becomes a modern cliché in clinical cancer treatments [74-78]. How to combine use of anticancer drugs is an emerging problem for anticancer drug therapy study [79,80]. Future trends will be discussed in later section.

### Assistant cancer therapy

Similarly, anticancer assistant therapy is also a useful way of therapeutic improvements, especially for some very refractory cancer types-solid tumors [25,26, 55-61]. In future, some new laws (what types of anticancer or antimetastatic drugs are the best combinations) remain to be elucidated. These types of medical findings must be repeatable and discovered by experimentally pharmacologic study and double-blind clinical evaluations [25,26]. These topics are the major pharmacological/therapeutic issues in clinical ICT/PCT trials.

### Patient's decision

In order to satisfy cancer patients and improve therapeutic outcomes, decision aids systems might also helpful in clinical therapeutics [27,28]. By providing decision aids service, cancer patients may be more cooperative and optimize for further clinical cancer therapeutics. This emerging technique may reach unexpected result in cancer treatments. This type of medical service might be added to future PCT/ICT items.

### Artificial intelligence in ICT/PCT

Artificial intelligence techniques might sooner or later go into hospitals. This important cancer treatment trend must be noticed early. Since repetitive therapeutic work or variability of doctor's prescriptions will be superseded by computers, robots and other artificial intelligence technology. Don't miss this milestone work in future.

### Economic consideration of ICT/PCT and cost-effective in clinical trials

Updating clinical cancer treatments is a difficulty and cost thing nowadays. Though it is a better way to benefit tumor growth/metastasis treatments by ICT/PCT, we still do not find any closer association between therapeutic benefits and therapeutic expenditures. A good balance between drug activity, toxicities and cost is the state-of-the-art system and new law of anticancer drug combination study. In order to do that, mathematical/computational network is the cheapest ways for simulations and decision-making. As a result, further work is needed in this avenue.

Since many ICT/PCT strategies are complementary with each other, two or three types of ICT strategies are seldom applicable in one cancer patient for economic considerations and technical feasibility. According to cancer patient' pathological situation and financial condition, we can optimize cancer therapeutics for patients in future [29-31]. However, selections of ICT/PCT must be based on cost-effective evaluations. Cost-effective study of drug combination and biotherapies, such as gene therapy or antibody therapy is main parts of ICT/PCT owing to their relatively higher therapeutic costs. Considering more than $10,000 expenditure of common cycles of drug combination/biotherapy, the cost of new types of ICT/PCT strategic options may be much less if we can maintain the diagnostic fee to $30 - 5,000. ICT/PCT of less than 5,000 USD is certainly cost-effectiveness. After new cost-effective diagnostics, it will certainly increase the quality adjusted life year (QALY) of cancer patients, especially in some early stage of cancer or young cancer patients [29-31]. Almost each of presently used ICT/PCT strategies is cost-effective from broader definitions and possibly save the life of more cancer patients.

### Comparisons of different items of ICT/PCT strategies

Since cancer treatments are far from our expectations and requirements-greatly elongation of cancer patient's survivals, ICT/PCT perfections is inevitable.

In order to improve currently available ICT/PCT strategies, new round of experimental/clinical campaign and ICT/PCT applications will be undergone. Presently, anticancer drug development is more suitable for human leukemia treatment and less effective to solid human tumors, especially to late-staged cancer patients. In future, more complex forms of ICT/PCT will be developed for cancer patients with solid tumors.

Among different types of ICT/PCT, which type of ICT/PCT strategy is the best? Each of them has its own advantages and disadvantage. At present no one type of ICT/PCT strategies is obviously advantageous over the others. In addition, no available ICT/PCT strategy has been well enough to significantly increase the patient's survivals comparing with conventional therapy. So, we desperately need some dramatic moves to create new generations of more matured ones by integrating the advantages of most ICT/PCT types. Although much effort has been made, main obstacles remain to be overcome. The most important drawbacks of these ICT/PCT strategies is there is almost no survival benefits in patients with noticeable metastatic nodules in spite of DST, PG and other item utilities [32-35]. But it can be a future miracle if we can perfect them into a successful one. So, are we ready for that yet? [81].

## Disease information modality

Cancer is a disease of great diversity of tumor genetic alterations or molecular abnormalities. Normally cancer can be categorized into 6 distinct hallmarks of pathologic processes (Table 1). The different ICT/PCT modalities are utilized for different hallmarks. It is proposed that different cancer hallmarks are suitable from different diagnostic modalities-PCT/ICT strategy.

| Hallmarks of cancer | Suitable PCT/ICT items or strategy |
|---|---|
| Sustaining proliferative signaling | DST, PG |
| Resisting cell death | Biomarkers |
| Inducing angiogenesis | Hormonal/assistant therapy, bioinformatics |
| Evading growth suppressors | PG |
| Enabling replicative immortality | PG, bioinformatics |
| Invasion and metastasis | Drug combination, assistant therapy |

***Table 1:*** *Schematic outlook of associations between biology and pathology mechanisms and ICP/PCT strategies.*

We have personally categorized these relationships into table 1. Following sectors will discuss other important items of PCT/ICT strategies.

Table 2 and 3 represents the technical cores of different types of ICT/PCT strategies nowadays (Table 2 and 3). From our vision, an integrated ICT/PCT strategy/paradigm will be designed from essence of these core technologies. Future biomedical efforts will offer these details and invite new items of ICT/PCT strategies with integrated technique and cutting-edge medical knowledge.

| Major strategy | DNA | RNA | Macromolecules | Bioassay |
|---|---|---|---|---|
| DST | √ | √ | √ | +++ |
| PG | +++ | + | + | √ |
| Bioinformatics | + | ++ | +++ | √ |
| Metastasis | √ | √ | ++ | ++ |
| Drug combinations | √ | √ | + | ++ |
| Hormonal/assistant | √ | √ | ++ | ++ |

***Table 2:*** *The associations between PCT strategies and biological suitability.*

***Symbolic Meaning*** *+ Some Suitability; ++ Good Suitability; +++Excellent Suitability; √Needs Future Improvements.*

| ICT strategies | Core techniques |
|---|---|
| DST | Cell number or viability |
| PG | SNP |
| Metastasis condition | Tomography |
| Bioinformatics | High-throughput techniques (omics) |
| Drug combinations | Pharmacology |
| Hormonal/assistant therapy | Drug characters |

***Table 3:*** *Technical cores of different ICT/PCT strategies nowadays.*

## Next Generation of ICT/PCT Strategies

### Integration is the key

One decade ago, we proposed that integrated ICT/PCT systems would be a future trend [5]. After more than one decade, we reiterate our past argument in this article with newest twist.

The good ICT/PCT strategies must contain multiple functionality/therapeutic information-including cancer property revealing, drug types/responsibility, mathematical/computational information treatments [82-86] and decision-aids system [27,28] to individual patients. Thus, future strategy of ICT/PCT must at least contain a process of drug response (pharmacology), tumor pathogenesis information (oncology) and others [87,88]. In the past, pharmacology (DST and drug combination) and tumor characters and pathologic processes (tumor bioinformatics, biomarkers and PG) are separately determined in the clinic. This situation needs to be improved. Certainly, more dramatic technical innovations, such as next generation sequence (NGS) [89] must be incorporated into new generations of ICT/PCT systems and strategies in future. Among these trends, computational network, patient's decision aids and artificial intelligence must be updated and integrated into one system of ICT/PCT.

Afterwards, ICT/PCT needs to be less and less moneys and multi-levels of medical/pharmacological information. New techniques might change the landscape or blueprint of ICT/PCT study and application scenarios. Some longstanding questions of cancer biology and pathology, such as relationship between cancer heterogeneity and different drug combination therapy might provide new foundation. High-resolution and lower cost ICT/PCT from technical innovations and medical/pharmacologic advancements might create growing usefulness of ICT/PCT strategies in the future (Figure 3).

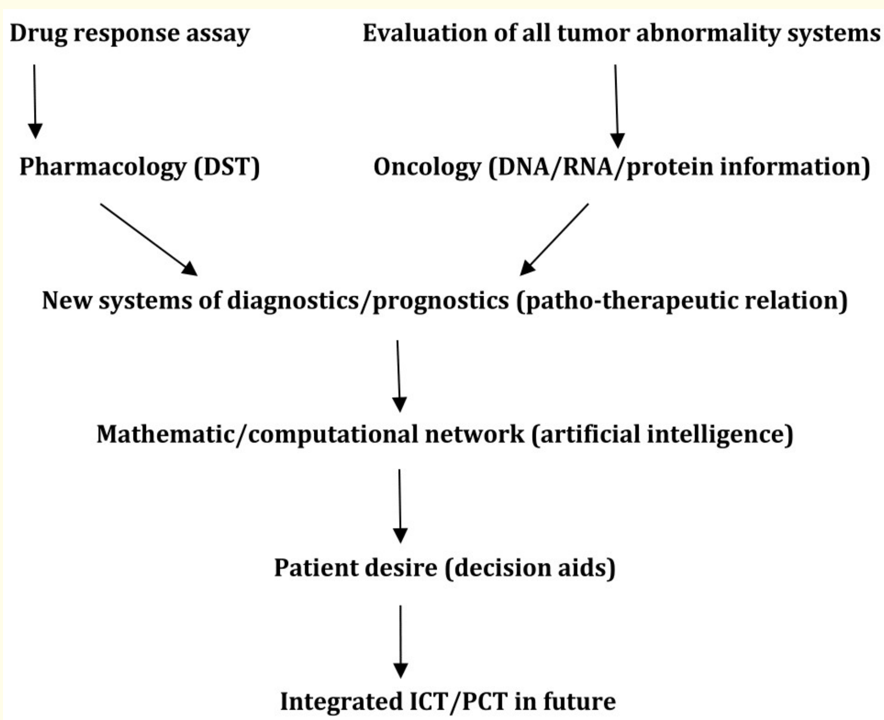


***Figure 3:*** *General scheme of ICT/PCT strategy developments in future.*

### Anticancer drug combination updating

Drug combination optimum strategy is too complicated to be easily mastered by clinical doctors. Though drug combination is a common way to enhance patients' therapeutic outcomes and survivals, there is still much room for updating and improving in both experimental and clinical investigations. In the past, clinical anticancer drug combination is based on doctors' judgment without in-depth therapeutic mechanism supporting. Clinical cancer combination therapies are generally empirical, statistics-oriented or past references rather than well-defined diagnostic/pharmacological association study. Finding new laws regarding anticancer drug combination (efficacy vs toxicity) must be established in future-central dogma establishments [74]. Due to highly complication from medical/pharmacologic situations, we cannot as usual overlook it [75].

The establishment of central dogma for drug combination is no easy task. In order to find this information, every possibility of drug combination must be undergone. Nowadays, approximately 178 anticancer drugs have been licensed worldwide [74-75],

According to mathematic equation (calculation for 2 - 3 anticancer drug combinations); (equation 1 - 2)

$C2 = (178\times177)/(1\times2)=15,753$ (equation 1)

$C3 = (178\times177\times176)/(1\times2\times3)=924,176$ (equation 2)

At the beginning of this study, we are awed with high numbers of drug combination possibility (Equation 1 and 2). However, when we think about the number of cancer morbidity worldwide, we are relieved suddenly [78]. Our conclusion is that only global coordination of this study can facilitate and master the core of drug combination practice (central dogma) sooner or later.

## Conclusion

ICT/PCT is a difficult approach [90]. In order to in depth understand cancer pathology and therapy for individual patients, well-defined, prospective, retrospective and double-blind ICT/PCT clinical studies and clinical applications are urgently needed. We look forward to some integrated ICT/PCT strategies to be established from empirical to scientific-guided systems. From our perspective of ICT/PCT innovations, integration is the key!

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## Competing Interesting

Authors have declared that no competing interests exist.

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