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Overview of Precision Oncology Trials: Challenges and Opportunities

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Abstract

Introduction—In recent years, the therapeutic management of selected patients with cancer has shifted towards the ‘Precision Medicine’ approach based on patient’s mechanisms of tumorigenesis, and their baseline characteristics and comorbidities. Complete tumor and cell-free DNA profiling using next-generation sequencing, proteomic and RNA analysis, and immune mechanisms should be taken into consideration and accurate bioinformatic analysis is essential to optimize patient’s treatment.

Areas covered—The challenges and opportunities of conducting clinical trials in precision oncology are summarized.

Expert commentary—Precision medicine has significantly changed the diagnostic and therapeutic landscape of cancer. Successful implementation of precision medicine requires translational and bioinformatics infrastructure to support optimization of treatment selection. Targeted therapy, immunotherapy, T-cell therapy alone or in combination with cytotoxic or other effective therapeutic strategies and innovative clinical trials with adaptive design should be offered to all patients. Data sharing and “N of 1” models hold the promise to optimize the treatment of individual patients and expedite drug approval for rare alterations and tumor types. Artificial intelligence will facilitate accurate utilization of sequencing data to perform algorithm analysis. Collaboration of health care providers with pharmaceutical and biotechnical companies, scientific organizations and governmental regulatory agencies have a crucial role in curing cancer.

Keywords

ctDNA; immunotherapy; molecular; mutation; N-of-1; personalized; precision; targeted; trial

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Declaration of Interest

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1. Introduction

Cancer therapy has shifted towards personalization of patient management in addition to developing treatments for specific tumor types. The evolving strategy of treatment selection using the precision medicine approach uses a patient's tumor and cell-free DNA analysis, immune markers and other biologic features and comorbidities to determine and offer optimal therapy to individual patients.

The identification of Philadelphia chromosome [t(9;22)] in patients with chronic myeloid leukemia (1) led to the discovery of imatinib mesylate, which was approved by the Food and Drug Administration (FDA) in 2002 for the treatment of newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (2). Following this example, ground-breaking discoveries in the field of genomics and high-throughput technologies have led to the identification of multiple molecular alterations and approval by the FDA of multiple targeted agents (3–9). Although initially the term “Precision Medicine” was used to describe targeting tumor molecular abnormalities with drugs that are known to inhibit the function of a molecular alteration, in recent years, this term includes immunotherapy and therapeutic agents that target any biological abnormality associated with carcinogenesis. In this review we summarize the challenges in implementation of precision medicine in Oncology.

2. Molecular testing

2.1. Next-generation sequencing (NGS) panels

Tumor NGS has accelerated the development of anticancer therapy. The improvement of NGS technologies enables the completion of tumor and cell-free molecular profiling more efficiently compared to older technologies. Comprehensive panels, with an increasing number of genes that include immune signatures and RNA profiling are currently being developed and used in clinical trials. In December 2017, the United States Food and Drug Administration (FDA) approved the use of a targeted NGS panel for patients with non-small cell lung cancer (NSCLC), melanoma, breast, colorectal and ovarian cancer (10). Approval of platform diagnostics, in contrast to the limited “drug-specific companion diagnostics”, will expedite the implementation of Precision Medicine, by allowing efficient tumor characterization.

2.2. Quality and standardization of next-generation sequencing data

Accuracy and reproducibility are essential aspects of molecular testing, particularly taking into consideration the large number of companies and institutions (reportedly, >150) that perform Clinical Laboratory Improvement Amendments (CLIA)-certified NGS in the United States. Standardization of sequencing methods, variant annotation and data interpretation should be continuously optimized. Recently, guidelines for validation and monitoring of targeted NGS panels (11) and interpretation and reporting of genomic variants have been proposed to ensure high quality of sequencing results in the clinical setting (12). Ideally, diagnosis of cancer should be followed by tumor whole genome sequencing (WGS), which provides comprehensive genetic information, including pathogenic alterations, as well as alterations of unknown clinical significance. High-quality, coordinated and cost-efficient

bioinformatics infrastructure is required to convert raw genomic data to clinically useful information for the therapeutic management of individual patients.

The cost of high-quality WGS for research purposes had reportedly significantly decreased from 15 million dollars (2006) to < \$1,500 (2016) (13). CLIA-certified WGS is not routinely used, mainly due to complexity of the experimental procedures, arduous data interpretation, and high cost. Collaborations between scientific and regulatory agencies will be needed to render WGS accessible to all patients at the time of diagnosis.

2.3. Cell-free DNA analysis and tumor heterogeneity

A major challenge in precision medicine trials is tumor heterogeneity. Due to significant heterogeneity between the tumor in the organ of origin and metastatic sites in selected patients, molecular profiling of tissue obtained from a single tumor lesion is not always representative of the systemic disease. Consequently, drugs targeting the molecular aberrations of one lesion might not be effective in all metastatic tumor lesions. More importantly, tumor molecular profile constantly evolves, particularly under the pressure of targeted treatments (14). The implementation of sequential biopsies to identify emerging molecular alterations is time consuming, costly and associated with biopsy-related risk. Genomic analysis of plasma cell-free DNA is emerging as a compelling approach for the detection and characterization of circulating tumor DNA (ctDNA). ctDNA genotyping is being developed as a cost-effective, non-invasive tool for tumor molecular profiling when the tumor is inaccessible or insufficient, when tumor biopsy is associated with a significant risk, and/or when serial tumor genotyping is needed to monitor the evolution of molecular abnormalities and optimize treatment. ctDNA analysis is thought to overcome the limitations associated with tumor tissue biopsy and are being used in selected clinical trials, although their use has not been systematically reported in prospective therapeutic oncology trials. The successful implementation of ctDNA analysis to assess driver mutations is best exemplified in NSCLC (15). Despite these promising results, technological challenges still exist. Most ctDNA assays are currently under development. Some CLIA-certified ctDNA tests that detect a small number of mutations are available, however, their clinical relevance and correlation with antitumor activity has not been determined. According to our recent joint review of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP), the evidence of clinical validity and utility for the majority of ctDNA assays in advanced cancer are insufficient (16). Additionally, results of ctDNA and tumor tissue genotyping analysis are at times discordant (16). CLIA-certified ctDNA tests are available and in clinical use. Prospective trials should generate high quality data to assess the clinical use of ctDNA analysis.

2.4. Mechanisms of resistance

Although selected patients have prolonged response to matched investigational drugs in precision medicine trials, the majority of patients eventually develop disease progression and succumb to their cancers. Some investigators have demonstrated that ctDNA analysis may detect emerging dominant cancer subclones prior to radiologic evidence of disease progression, indicating mechanisms of acquired resistance to treatment in real time, and conceivably providing opportunities for early therapeutic intervention and novel drug

development. In September 2016, the FDA approved a clinically validated blood-based companion diagnostic test, which detects the presence of T790M point mutations in patients with EGFR-mutant NSCLC, after disease progression on an EGFR tyrosine kinase inhibitor (17). Osimertinib, a drug targeting an acquired mutation improved significantly the outcomes of EGFR-mutant patients with NSCLC resistant to first- and second-generation EGFR inhibitors (18). The role of ctDNA analysis in assessing mechanisms of drug resistance is being explored in various tumor types (19–21) and sequential ctDNA may provide insights regarding evolution of tumorigenesis and disease progression.

3. Bioinformatic analysis

3.1. Bioinformatics and complete understanding of driving alterations in carcinogenesis

Bioinformatic analysis is an essential part of Precision Medicine. “Oncogene addiction”, first reported in 2002, describes the dependence of tumor cell survival on a particular molecular alteration (22). The identification of “driver” molecular alterations among “passenger” abnormalities, has revealed several drug targets. Therapeutic intervention may be complicated when >1 targetable molecular alterations are identified. The functional role of these “driver” mutations particularly in relevance to concomitant networking alterations taking into consideration the tumor histology. Since therapeutic decisions are based on tumor molecular profiling, the analysis should be performed in a timely manner. Results are usually available at the minimum in 2 weeks, although a 1–3 day time period would be optimal. Therefore, innovative bio-analytical methods are warranted to expedite completion of molecular profiling in the shortest period of time possible.

3.2. Artificial intelligence (AI) and learning algorithms

“Big data”, i.e. the massive amounts of genomic data generated by high throughput profiling, characterized by Velocity, Volume, Value, Variety and Veracity (5 “Vs”) cannot be processed using conventional methods and require AI and machine-learning algorithms (23, 24). Using the available clinical knowledge, computational technologies are being developed to identify diagnostic and therapeutic algorithms (25). For instance, IBM (International Business Machines)’s Watson for Oncology, is an AI system, that can analyze data from clinical notes, article and scientific reports, including guidelines from the National Comprehensive Cancer Network (NCCN) Clinical Practice in Oncology (26). Combining these data with patients’ records, the program suggests evidence-based, personalized treatment plans for individual patients. The combination of AI-obtained diagnostic algorithm with physicians’ interpretation is reportedly associated with a diagnostic accuracy of 99.5% (27).

3.3. Data sharing

Data sharing is critical for the scientific progress in precision medicine, but it is limited due to legal, ethical, financial, and technical concerns. Many organizations are restricted in sharing essential data due to confidentiality agreements with pharmaceutical and biotechnology companies and associated difficulty in publication of their results and obtaining funding, if confidential, unpublished data are shared. Despite these challenges, sharing accurate molecular, pharmacologic, clinical, and treatment outcome data,

particularly for rare genomic alterations and efficacy of selected drugs, will accelerate discoveries in precision medicine research. Scientific organizations have created platforms to facilitate data sharing (28). The National Cancer Institute (NCI) has created the Genomic Data Commons, a unified data repository system for storage and analysis of data, that enables genomic and clinical data sharing across cancer genomic studies to support precision medicine (29). The American Association of Cancer Research (AACR) launched Project GENIE (Genomics, Evidence, Neoplasia, Information, Exchange), an international data-sharing registry that aggregates and links CLIA-certified genomic data, obtained at routine practice, with clinical outcomes from patients with cancer treated at various institutions. (30). ASCO's CancerLinQ (Learning Intelligence Network for Quality (Alexandria, Virginia), a data-sharing learning health system for oncology aggregates de-identified data from electronic health records (31). The CancerLinQ data represent "real-world evidence (RWE)", defined as a source other than a clinical trial, and include a public resource available to the academic and community researchers, public health agencies, life sciences organizations and patient advocacy groups (31). As significant resources have been dedicated to these initiatives, complete and accurate data of patient baseline characteristics, genetic profiling, treatment and patient outcomes are essential for robust analyses. Paradigm shift in Precision Medicine through these initiatives remains to be seen.

4. Clinical trials

4.1. Study design

Phase III randomized trials are considered the gold-standard for approval of a novel agent. However, these studies are cumbersome, expensive and lengthy and the comparator arm is often suboptimal (e.g., placebo or not the most effective available treatment). More importantly, with the large variability in patients' tumor markers, microenvironment, baseline characteristics, comorbidities and other covariates, even the best designed studies cannot account for all differences in the randomized arms, resulting in imbalanced groups, as every patient has unique features. The reported success of randomized clinical studies in oncology is approximately 38% (32, 33). The use of phase II studies with innovative design, including randomized ones, adaptive-design trials, "basket" or "umbrella", and "N-of-1" trials are thought to be more efficient in drug development.

Trials with adaptive-design are dynamically evolving and allow the randomization ratio to be modified, treatment arms with inferior outcomes to be eliminated, and biomarker selection to be optimized, according to up-to-date clinical outcomes generated by the study (34). Outcome data are used to adjust the randomization ratio, resulting in a higher proportion of patients to be randomly assigned to the treatment arm(s) that appear to be more effective. These trials use fewer patients and shorter-term treatment outcomes and appear to be time- and cost-efficient in drug development. For instance, outcome-adaptive randomization was utilized at the I-SPY 2 (Investigation of Serial Studies to Predict your Therapeutic Response with Imaging and Molecular Analysis 2) trial, a phase II trial, in which experimental agents were tested against control treatments in the neoadjuvant setting in patients with breast cancer (35). The FOCUS4 (Molecular selection of therapy in colorectal cancer: a molecularly stratified randomized controlled trial program) trial evaluates patients with

advanced, metastatic colorectal cancer whose disease is stable or responds to first-line chemotherapy, who are assigned to one of five sub-studies for randomization to a targeted agent (vs. control) based on tumor biomarkers (36). Finally, the Lung-MAP (Lung Master Protocol) trial has a different overall design. Specifically, a drug that is found to be effective in phase 2 will move directly into phase 3, incorporating the patients from phase 2, thus reducing time and resources (37).

In “N-of-1” trials, each patient is considered the sole unit of observation taking into consideration tumor genomic and molecular characteristics. The goal is to determine the optimal treatment for each patient using distinct tumor characteristics. In a modified “N-of-1” study design, the antitumor activity of anticancer agents matched to patients’ genotype was assessed (38). Of 86 heavily pretreated patients with refractory metastatic tumors, 66 were treated according to their molecular profiling and progression-free survival (PFS) was longer with the targeted treatment compared to PFS associated with their previous systemic treatment. The “N-of-1” studies could be informative for low-prevalence molecular aberrations, when randomized studies are difficult. Columbia University labeled “N-of-1”, a clinical personalized trial in 13 tumor types. In this study, tumor whole-genome sequencing and RNA expression analysis suggests drugs that target the identified molecular abnormalities that are tested *in vitro* and *in vivo*. If treatment appears effective, physicians are informed to optimize patients’ therapeutic management (39).

4.2. Drug availability

The development of drugs that effectively inhibit the function of pathogenic molecular alterations is suboptimal. Currently, the armamentarium of drugs to effectively treat patients with all known driver alterations is limited, although the number of pathogenic alterations is increasing (40). There are very few drugs targeting rare alterations and tumor types (41). Providing incentives and encouraging collaboration between regulatory agencies, investigators, pharmaceutical and biotechnology companies may increase the development of drugs for rare diseases.

4.3. Prospective and Randomized Clinical Trials Across Tumor Types

In 2007, we initiated the first Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) study (42, 43). In a retrospective analysis of prospectively molecularly profiled patients with advanced cancer, we demonstrated that tumor molecular profiling and selection of matched targeted therapy is associated with higher rates of response, PFS and overall survival (OS) compared to patients not treated with matched targeted therapy. In the matched targeted therapy group, PFS was longer in patients than the PFS of the same patients’ prior systemic therapy (42–44). Following the encouraging results from the first IMPACT study, in 2014 we initiated IMPACT 2, a randomized study evaluating molecular profiling and targeted therapy in metastatic cancer (45, 46). The primary objective of this study is to determine whether patients with advanced cancer who are treated with matched targeted therapy, selected based on genomic tumor profiling, have longer PFS than those whose treatment is not selected based on their molecular profile.

The first randomized study in Precision Oncology in advanced cancer was the SHIVA trial, which assessed molecularly targeted therapy based on tumor molecular profiling versus conventional therapy (47). The endpoint of the study was PFS. This trial included targeted drugs, which were available in France in 2011. No difference in PFS was noted between the two groups (47). The trial had several limitations (48). Patients with several molecular aberrations, were less likely to respond to monotherapy and pretreated patients with advanced disease were less likely to respond to hormone monotherapy, matched to hormone receptor abnormalities. Some matches between the molecular abnormalities and targeted treatments were inaccurate. Biological data were not used in the context of clinical experience, for many of the matches in the SHIVA trial. Finally, treatment assignments were based on a predefined algorithm in the group that received matched targeted therapies, in contrast to the control group, where the assignments were performed by the treating physician. To implement precision medicine, a targeted drug should be carefully chosen to effectively and consistently inhibit the function of a “driver” molecular alteration. Clinical experience needs to be combined with genomic data to successfully select targeted therapy, including combinations, targeting molecular alterations.

Based on the encouraging results of our first IMPACT trial and evolving data from collaborating institutions assessing tumor RNA profiling, in 2012 we initiated the WINTHER trial in 5 countries through the Worldwide Innovative Network Consortium for personalized cancer therapy to “select rational therapeutics based on the analysis of matched tumor and normal biopsies in subjects with advanced malignancies” (49). The primary endpoint of the study was the ratio of PFS using a treatment based on the molecular analysis of a patient’s tumor compared to PFS of the most recent regimen on which the patient had experienced progression. The investigators experienced several challenges of conducting this study, including limitations in gaining access to matched targeted therapy, establishing regulatory oversight in all participating countries and managing cost issues.

Following the example of the IMPACT2 study (46), several clinical trials were initiated across tumor types (50–52). The NCI launched the NCI-MPACT (Molecular Profiling-Based Assignment of Cancer Therapy) study to compare the response rate and the 4-month PFS of patients treated with agents selected based on tumor molecular alterations and patients treated with drug not known to target the alterations of interest (51). Between February 2014 and July 2015, 60 patients with solid tumors were enrolled in the NCI-MPACT trial, including 8 with sarcoma and treatment was assigned to 29 (52%) patients (53). In August 2015, the NCI initiated the MATCH (Molecular Analysis for Therapy Choice) trial, which included single-arm phase II studies matching molecular abnormalities to agents that target specific abnormalities (50). The initial plan was to screen 3,000 patients, but after the interim analysis, 6,000 patients were to be enrolled in 1,100 participating sites. Although the study drug was provided at no cost to patients, relatively very few patients were treated. Results of four arms were reported (54–57). The use of the PI3-kinase inhibitor, taselisib, was associated with PFS 6 months in 27% of patients with activating mutations in the PIK3CA gene and mixed histologies (54). The use of ado-trastuzumab emtansine (T-DM1) in patients with HER2-overexpressing tumors, excluding breast and gastric/gastroesophageal junction cancers resulted in a partial response (PR) rate of 8.1% (3 of 37) and stable disease (SD) rate of 43% (17 of 37; median duration, 4.6 months) (55). The 6-

month PFS rate was 24.8% (90% CI 15.0%–41.1%). The PR rate in patients with alterations in the fibroblast growth factor receptor (FGFR) pathway treated with the selective FGFR inhibitor AZD4547 (N = 41) was 5% and the SD rate 51% (56). The 6-month PFS rate was 17% (90% CI: 8.6–34%). Finally, the use of the programmed cell death 1 (PD1) inhibitor (nivolumab) resulted in an objective response of 24% (8 of 33) in patients with relapsed or refractory non-colorectal mismatch repair deficient (dMMR) cancers and the estimated 6-month PFS was 43% (57).

ASCO's TAPUR (Targeted Agent and Profiling Utilization Registry) study is also investigating the efficacy of currently used drugs in various tumor types harboring a genomic variant known to be a drug target (52). This non-randomized clinical trial assesses response associated with the use of off-label FDA-approved targeted treatments in advanced cancer. It is being conducted in collaboration with pharmaceutical companies and multiple institutions and practices. Treatments are provided at no cost to patients and participating institutions provide clinical outcome data in return (52). TAPUR's expansion in Europe, Drug Rediscovery Protocol (DRUP) also assesses efficacy and toxicity of commercially available, targeted anticancer drugs across tumor types based on tumor profile (58). The French National Cancer Institute designed the AcSé (Accès sécurisé à des thérapies ciblées innovantes) program to evaluate the efficacy of targeted drugs used outside of approved indications (59). In 2016, >7,000 patients were enrolled in AcSé-led trials in 183 sites.

4.4. Other national and world-wide collaborations

With the exception of pharmaceutical and biotechnology companies, precision medicine research is accomplished by funding from the government, donors, and scientific communities. The National Institutes of Health (NIH) and the NCI focus on precision medicine trials. In 2016, the Congress authorized \$1.8 billion to fund the Cancer Moonshot initiative (60), while the NIH announced \$55 million in awards to expand the Precision Medicine Initiative Cohort Program (61). The program aimed to establish partnerships and infrastructure to support research on the prevention and treatment of cancer based on individual differences in lifestyle, environment and genetics. To date, the NCI sponsors several precision medicine trials, including the NCI-MATCH, ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials) Lung-MAP and NCI-MPACT (62).

The European Union is also enhancing research funding programs for precision medicine, through the Seventh Framework Program (63), Horizon 2020 and the Innovative Medicines Initiative (64). A patient-centered infrastructure of six major European cancer centers, Cancer Core Europe, aims to develop personalized cancer medicine using novel diagnostics and therapeutics and conducting next-generation clinical trials with data sharing capability (65).

5. Immunotherapy and T-cell therapy

The use of immunotherapy in implementation of precision oncology is thought to overcome the complexity of molecular profiling, by initiating an immune response against patients' tumors (66, 67). Multiple novel immuno-oncology treatments are being explored, including

modified cytokines, cell-based products, oncolytic viruses, CD3-bispecific antibodies, and vaccine platforms. As of January 2018, >1,700 clinical trials of immunotherapeutic agents as monotherapy or combined with other drugs are being conducted, aiming to enhance the host immune system against tumor cells and to overcome resistance, inducing durable responses. In 2017, the FDA approved the PD1 inhibitor pembrolizumab based on immune markers associated with response across tumor types and for selected tumor types. Pembrolizumab is approved for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or dMMR solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options, and for patients with MSI-H or dMMR colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan (68). Pembrolizumab is also approved for Programmed death-ligand 1 (PD-L1)-positive recurrent or advanced gastric or gastroesophageal junction adenocarcinoma with 2 lines of chemotherapy, including fluoropyrimidine- and platinum-containing chemotherapy, and, if appropriate, HER2/neu-targeted therapy. The successful example of tumor agnostic approval of a PD1 inhibitor (68) should be followed by accelerated drug approval of other drugs, based on tumor response and robust biomarkers, across tumor types.

High tumor mutational burden (TMB) has been used as a genomic biomarker to identify patients likely to respond to immunotherapeutic agents. Some investigators have reported that high TMB has been independently associated with improved clinical outcomes in diverse tumor types (67). Others demonstrated that higher somatic nonsynonymous mutation burden was associated with clinical efficacy of a PD1 inhibitor (pembrolizumab) in patients NSCLC (66). The antitumor activity of PD1 and cytotoxic T lymphocyte-associated protein 4 (CTLA4) inhibitors has also been associated with high TMB in patients with small-cell lung cancer (69). However, there are several questions that remain to be addressed regarding the use of TMB as a predictive biomarker for immunotherapeutic agents, including standardization of the definition of high TMB, its harmonization across different NGS platforms and the prospective validation of its clinical significance in tumors excluding lung cancer and across tumor types.

A field of increasing interest due to the induction of durable responses in selected hematologic malignancies is adoptive T-cell therapy, which enables the genetic reprogramming of T-lymphocytes to recognize tumor specific antigens (70). We have initiated a clinical trial, ACTolog (Adoptive Cellular Therapy Trial With Endogenous CD8+ T-cells) for patients with relapsed/refractory solid tumors using engineered autologous CD8+ T-cell products, target-specific for each patient's tumor cells (71).

6. Conclusions

Implementing clinical trials in precision oncology involves several challenges (Table 1). The ultimate goal is the ability to use in all patients at the time of diagnosis their tumor genomic profiling, immune markers and other biological features to determine optimal treatment. Innovative clinical trial designs that incorporate the dynamic biological changes and the complexity of cancer are needed. The technological evolution and the evaluation of "big genomic data" warrant the use of robust bioinformatics and AI infrastructure. Collaboration

of health care providers with pharmaceutical and biotechnical companies, scientific organizations and governmental regulatory agencies plays a crucial role in curing cancer.

7. Expert commentary

Advancements in biotechnology, identification of mechanisms of carcinogenesis and discovery of novel strategies, including matched targeted agents and immunotherapy, have revolutionized cancer therapy with unprecedented improvement in patient outcomes. Understanding genomic, transcriptomic, and proteomic alterations as well as immune mechanisms enables optimization of treatment selection for individual patients. Complete tumor and cell-free DNA profiling using NGS, proteomics, RNA analysis and understanding of the immune mechanisms should replace “companion diagnostic tests”, which are inefficient and limited. Bioinformatic analysis remains essential for accurate diagnosis. Combinations of anticancer agents should replace single agent treatment in most patients, because one anticancer agent cannot effectively eradicate cancer in all patients. Innovative clinical trials with adaptive design should be offered to all patients. These designs should incorporate treatments targeting dynamic changes in tumor biologic abnormalities, eliminating minimal residual disease, and eradicating significant subclones conferring tumor resistance to treatment.

8. Five-year view

In the next five years, we will accelerate the implementation Precision Medicine by complete identification of mechanisms of carcinogenesis for every patient, discovery of novel drugs, and using personalized therapy that effectively inhibits the function of the driver biologic alterations to all patients with cancer. Targeted therapy, immunotherapy, T-cell therapy alone or in combination with cytotoxic or other effective therapeutic strategies will be offered to all patients and have the potential to cure cancer. Data sharing and “N of 1” models hold the promise to optimize the treatment of individual patients and to expedite drug approval for rare alterations and tumor types. AI will facilitate accurate utilization of NGS data to perform algorithm analysis leading to optimal drug selection, for all patients in a timely manner. Scientific and governmental agencies have a crucial role in preparing the informational infrastructure for the use of AI in patient care and to provide the required resources to cure cancer.

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9.

Key issues

- Precision medicine uses a patient's molecular and biologic features, including immune markers to determine optimal therapy and drugs known to inhibit the mechanisms involved in carcinogenesis of individual patients. This therapeutic approach should be available to all patients at the time of diagnosis and throughout the course of their disease.
- Complete tumor and cell-free DNA profiling using next-generation sequencing, exome sequencing, proteomics, RNA analysis and understanding of the immune mechanisms hold the promise of complete characterization of drivers of carcinogenesis. These tests should replace "companion diagnostic tests", which are inefficient and limited.
- Accurate bioinformatic analysis remains essential in understanding tumorigenesis in individual patients.
- Combinations of anticancer agents should replace single agent treatment in most patients.
- Targeted therapy, immunotherapy, T-cell therapy alone or in combination with cytotoxic or other effective therapeutic strategies and innovative clinical trials with adaptive design should be offered to all patients.
- Data sharing and "N of 1" models hold the promise to optimize the treatment of individual patients and to expedite drug approval for rare alterations and tumor types.
- AI will facilitate accurate utilization of NGS data to perform algorithm analysis.
- Collaboration of health care providers with pharmaceutical and biotechnical companies, scientific organizations and governmental regulatory agencies plays a crucial role in curing cancer.

Table 1:**Challenges and Opportunities in Precision Oncology**

Challenges		Opportunities
Molecular profiling		
Tumor biopsy	Not standard	Standard of care
Tumor sequencing	Targeted NGS	Whole Genome Sequencing in CLIA-certified laboratories
Bioinformatics (driver vs. passenger alteration)	Limited	Optimized
Molecular analysis, results	10 days	1–3 days
Tumor heterogeneity	Single lesion biopsy	Cell-free DNA analysis
Emergence of resistance to treatment	Limited data	Sequential tumor biopsies/ cell-free DNA analysis for real-time monitoring
Other		
Study design	Phase I, II, III	Adaptive design, “N of 1”, umbrella protocols
Drug availability	Limited drugs	Drugs for all identified alterations, including targeting immune mechanisms
Predictive biomarkers	Unavailable for all patients	Optimization of technology to identify clinically relevant markers for all patients
Patient eligibility	≈5–30% of patients	100% of patients
Funding	High cost, usually industry-sponsored	Additional government, donor, and scientific communities
Genome data analysis	Standard	Optimized bioinformatic analysis and artificial intelligence