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Q&A

The Use of Targeted Therapies for Precision Medicine in Oncology

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Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle to develop an individualized treatment plan. It was brought to the forefront recently as President Barack Obama launched the Precision Medicine Initiative, which aims to revolutionize medicine and move the concept of precision medicine into everyday clinical practice with near-term goals focused on cancer. Clinical applications that will benefit from precision medicine include improving patient diagnosis and prognosis, predicting treatment response, and determining predisposition to certain cancers. This information will be incorporated into an individualized patient treatment plan that will provide maximum benefit while reducing the use of drugs that have serious side effects and are unlikely to benefit the patient. In addition to improving patient survival and quality of life, there will be an overall reduction in cost for the healthcare system.

Targeted therapy provides the foundation of precision medicine. Even in individuals with similar clinical cancer phenotypes, drug therapy is only effective in a subset of patients. Owing to recent advances in molecular biology, genomics, and bioinformatics, research has shown that differential drug response is often a result of differences in genetic alterations. Altered genes may contribute to cancer progression by allowing growth and spread of the malignancy. Alternatively, they may contribute to drug effectiveness if there are mutations in genes involved in drug metabolism. An in-depth understanding of the biology of the tumor, including molecular changes and altered signaling pathways will allow for the identification of patients who are likely to benefit from such treatments; it also may facilitate the development of new targeted therapies, which counter the influence of the specific molecular drivers contributing to the growth and spread of the malignancy.

In this Q&A article, 5 experts discuss the applications of precision medicine and how targeted therapy contributes to the overall goal of precision medicine in cancer patient management. They also address some of the challenges we face in the implementation of precision cancer therapy.

The hope for precision medicine is that treatments will one day be tailored to the genetic alterations in each person's cancer. For what cancer types do you think precision medicine will have the highest impact?

George M. Yousef: In order for precision medicine to have a significant impact on patient outcome, there should be a focus on: (*a*) cancers with high prevalence that represent an economic burden; and (*b*) cancers with known "trunk" mutations [according to the trunk-branch model of tumor heterogeneity] that can be targeted for therapy. Colorectal and cervical cancers are good examples. Moreover, genomic medicine will be able to subclassify cancers into specific biological subgroups with unique pathogenesis. Each subset will be a candidate for specific therapy that targets its specific pathogenic pathways. Lung cancer represents a good model in this regard, as distinct biological subtypes continue to be identified for treatment purposes.

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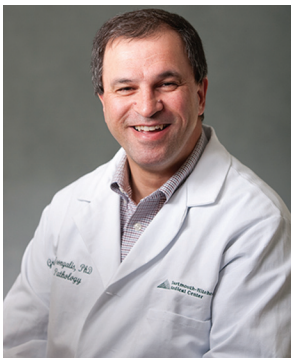
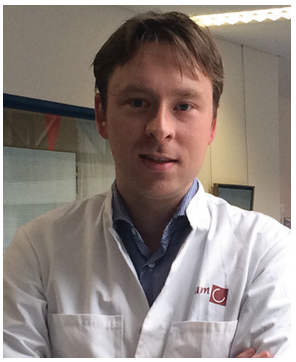


Gregory J. Tsongalis: President Obama's declaration of new initiatives in precision medicine, including the Moonshot Program to Cure Cancer, underscores the significant impact cancer continues to have on healthcare systems and wellness around the world. Precision medicine has acquired numerous meanings over the years and if we expand it to include not just therapies targeted to tumors with specific genetic variants but also to tumors that express specific mutant proteins or exhibit abnormal pathways, then we begin to impact all tumors. Early targeted therapies for cancer included assessment of the estrogen receptor in breast cancer. Today's targeted therapies include specific monoclonal antibodies such as trastuzumab for breast cancer and panitumumab for colon cancer, small molecule tyrosine kinase inhibitors such as imatinib for chronic myeloid leukemia (CML)[9] and erlotinib for lung adenocarcinoma, and immunotherapies such as pembrolizumab as a PD-1 (programmed death-1) inhibitor in metastatic melanoma.

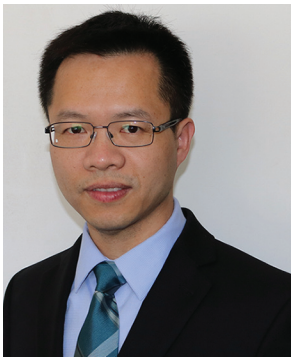
The first solid tumor type for proof of principle of precision medicine was breast cancer for the therapies mentioned above. More recently, lung adenocarcinoma, colon cancer, and melanoma have been considerably impacted by precision medicine efforts. As precision medicine concepts become refined and therapeutic efficacy better understood, cancer patients will benefit from the use of new therapies as indicated by the Food and Drug Administration (FDA) and through clinical trials and off-label use of these same therapies. For example, we are beginning to see treatment strategies that include the use of an FDA-approved drug for one tumor type with a particular genetic variant in a different tumor type having the same variant. In this respect, no human cancer should go unaffected by novel treatment approaches.

Louis Vermeulen: Precision medicine will be most effective in malignancies that are characterized by only a few strong driver mutations or genomic translocation events. These types of malignancies could be considered "honest" cancers. It will be much more challenging to develop effective targeted interventions for more complicated diseases with many drivers, and a relatively long and slow process of oncogenesis in which genetic aberrations accumulate and cells display complicated epigenetic rewiring. Examples of such "complex" malignancies are advanced breast cancer and lifestyle-associated colorectal and lung cancers.



Indeed, the most effective targeted interventions today corroborate this notion. Imatinib displays extreme efficacy in both CML, by targeting the single required and sufficient driving kinase ABL, and in *CD117*[10] [synonym for *KIT* (KIT proto-oncogene receptor tyrosine kinase)] mutant gastrointestinal stromal tumors, by inhibition of crucial c-kit kinase activity. Furthermore, targeted therapies are very effective in nonsmoking associated lung cancers displaying *EGFR* (epidermal growth factor receptor) mutations or *ALK* (anaplastic lymphoma receptor tyrosine kinase) rearrangements, but much less so in their smoking associated counterparts.

Encouragingly, an increasing number of driver events are identified that often occur in very rare subsets of cancers. Examples of these include *HER2* [synonym for *EBBR2* (erb-b2 receptor tyrosine kinase 2)] amplification in gastric cancers that can be targeted with trastuzumab, and the recently described RSPO (R-spondin) fusion events that occur in a small percentage of colon cancers and can be targeted by anti–R-spondin antibodies.



Ziqiang Zhu: Lung cancer is the leading cause of death among all cancer patients. Great efforts have been focused on both basic and clinical research of lung cancer, especially NSCLC (non–small-cell lung cancer). This work has been leading the way in the advances of precision medicine. A majority of the mutations discovered in lung cancer are actionable with either an approved drug or a drug in clinical trials.

[9] Nonstandard abbreviations: CML, chronic myeloid leukemia; FDA, Food and Drug Administration; cfDNA, cell-free DNA; FAP, familial adenomatous polyposis; miRNA, microRNA.

[10] Human genes: *CD117*, synonym for *KIT* (KIT proto-oncogene receptor tyrosine kinase); *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma receptor tyrosine kinase; *HER2*, synonym for *EBBR2* (erb-b2 receptor tyrosine kinase 2); *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *KRAS*, KRAS proto-oncogene, GTPase; *CEBPA*, CCAAT/enhancer binding protein alpha; *APC*, APC, WNT signaling pathway regulator; *RB1*, RB transcriptional corepressor 1; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

So far, more new drugs have been approved for lung cancer treatment in the past few years than in the past half century. Therefore, precision cancer therapy has already transformed the management of lung cancer.

Furthermore, I believe that in the near future, the question is not where the disease originates from, but rather, which specific cancer-driving mutation(s) it harbors—and information like this will drive precision medicine. Therefore, with the advances in genetic sequencing, detecting the genetic mutations that drive tumor growth and further targeting them will transform the management of the majority of the cancer types and eventually lead to a cure.

Suzanne Kamel-Reid: There are several different scenarios in which precision medicine will have the highest impact, depending on the context/definition of the term "precision medicine." When we consider precision medicine as "the right drug for the right person at the right dose," we can apply precision medicine through targeted therapies. The benefit of this approach has already been realized in cancers with targetable variants/mutations, e.g., *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) in melanoma; *EGFR* in lung cancer. However, when we consider precision medicine through prediction of response to established therapies, we are able to use molecular information to exclude or include a patient from treatment with conventional therapies [e.g., *KRAS* (KRAS proto-oncogene, GTPase) mutation in colorectal cancer; *CEBPA* (CCAAT/enhancer binding protein alpha) double mutant in allogenic stem cell transplantation; genetic causes of drug resistance). We can also apply precision medicine as an approach to enable the use of information derived from profiling a patient's disease site to manage patient care in a more refined way. This method enables us to clarify diagnosis based upon the presence of molecular data, or to modify the frequency of patient follow-up based upon the presence of potential prognostic markers.

Precision medicine depends on the current state of knowledge and is dynamic in nature (as it changes over time). It is important to distinguish between the current and future states of knowledge, and understand the potential for evolution of understanding based on technological advances in molecular profiling and screening methodologies, as well as growth in our knowledge of the cancer genome.

Tumor heterogeneity is a common phenomenon. Although patients may have tumors that appear morphologically similar, the underlying molecular makeup of the tumor may be quite varied. How could tumor heterogeneity impact the effectiveness of targeted therapy?

George M. Yousef: Besides impacting the effectiveness of targeted therapies, as explained by the other experts, tumor heterogeneity can also have a serious impact on the validity of the data produced by molecular profiling. Both intratumor heterogeneity and patient heterogeneity are important. This is particularly important in larger tumors. Strategies to overcome these limitations include multiple tumor sampling, focusing on pathways rather than individual molecules, and looking for circulating tumor markers (for example cell-free DNA [cfDNA]) that are hypothesized to provide a more comprehensive representation of the entire tumor.

Gregory J. Tsongalis: Our understanding of cancer as a clonal disease needs to be readdressed. To a certain extent cancer remains a clonal disease, but not to the extent that we all thought. Clearly, tumor heterogeneity can occur at cellular and molecular levels. Many tumors are composed of different cell types and this can impact the analytical aspects of somatic mutation testing. The molecular heterogeneity of these tumor cells has and will continue to impact therapeutic response. Our ability to detect mutations in subclones introduces novel clinical management questions regarding the cell population that should be treated. Clones characterized by different mutations may not all respond similarly to the same treatment. Furthermore, some mutations may potentially predict relapse of disease and/or resistance to treatment.

The clinical challenge that this poses is not unprecedented. In the early 1990s, clinicians faced a similar problem with the HIV-1 and AIDS epidemic. The ability of the virus to mutate or the initial presence of viral populations with different genotypes made the disease difficult to combat with one drug at a time. Similar to HIV-1, we *must* approach cancer with multitherapy cocktails that will inhibit multiple pathways simultaneously. This aggressive approach will better destroy subclones of tumor cells that have numerous variants and be less likely to result in relapse or metastatic disease with resistance.

The complexity of this issue is the most likely reason that new trials for novel therapies are not showing the significant positive outcomes that we had hoped. New models for clinical trials are needed and designs of future clinical trials must take into account the diverse variant spectrum of tumor cells and not focus on only 1 common variant. To this end, basket trials that include tumors of many different types with a common therapeutic target

or umbrella trials where a specific tumor type is treated with different therapies based on the molecular profile are becoming the norm and could help us better understand treatment response. In addition, randomized crossover trials may help better facilitate the introduction of combination therapies. These types of innovative clinical trial designs highlight the complexity of cancer as a disease and require extensive reconsideration of our treatment strategies.

Louis Vermeulen: Appreciation of tumor heterogeneity is key in understanding the activity of targeted agents. The genetic background of cancers to a great extent determines the efficacy of these drugs. In fact, optimal activities of targeted drugs are seen in those cases where the primary oncogenic activity is inhibited. For example, in lung cancers EGFR inhibitors are mostly active in tumors in which this gene is mutated and thereby constitutes a driver event.

Additionally, the genetics of cancers are pivotal to explain failure of targeted drugs. Many mutations conveying resistance to targeted agents have been reported. For example anti-EGFR antibodies are ineffective in colon cancers harboring an activating mutation in the RAS pathway that is situated downstream of EGFR. Currently, patients presenting with such mutations are excluded from receiving these drugs.

But there is more. Unfortunately, genetics alone cannot explain everything. In the last few years, it has become increasingly apparent that the context in which mutations occur, for example the tissue origin or the cancer subtype, are of great importance as well. It has been established that key driver events occurring in different malignancies respond differently to inhibition. A prime example of this concept is *BRAF* mutations and BRAF inhibitors. The *BRAF* V600E mutation occurs in approximately 50% of melanomas, and these tumors display remarkable response to BRAF inhibitory drugs. However, in colon cancers that present with the exact same mutation, these agents are largely ineffective. So, the same driver mutation, but a different tissue context results in greatly disparate drug efficacy. It has now been established that colon epithelial cells have different wiring of signal transduction cascades and that in this background, BRAF inhibition results in a rapid activation of EGFR and PI3K (phosphoinositide 3-kinase) signaling, thereby annihilating the effect of BRAF inhibition. This loop does not exist in melanocytes.

Ziqiang Zhu: Tumor heterogeneity includes phenotypic heterogeneity as well as genotypic diversity. This phenomenon introduces significant challenges in designing effective treatment strategies. Tumor cells usually bear multiple different mutations; therefore, combination therapy utilizing novel drugs that target multiple components of driver signaling pathways should be tailored to fit the genetic interactions. However, sometimes it is difficult to identify which one is the cancer-driving mutation. In many situations, even if a cancer-driving mutation is identified, the patient may still not be able to benefit if there is no existing targeted drug therapy. In addition, tumor heterogeneity may cause treatment failure due to drug resistance. Nevertheless, genomic approaches are revealing a tremendous amount of information to aid our understanding of cancer signaling, diagnosis and treatment.

Suzanne Kamel-Reid: Tumor heterogeneity may impact the effectiveness of targeted therapy in at least 3 ways. First, the "target" may not be present in all cells of the tumor, and therefore, therapy may not work for a significant proportion of cells within the cancer. Second, resistant clones containing specific molecular alterations, such as EGFR T790M in lung adenocarcinoma, which is associated with acquired resistance to tyrosine kinase inhibitor therapy, would render targeted therapy ineffective. Third, the cancer stem cell may not yet carry the targetable variant or may be resistant to conventional treatment due to various factors including quiescence or compartmentalization.

Initially, successful cancer therapies are often limited in time by the development of drug resistance. Resistance to targeted therapies can arise from selective growth of preexisting subclones within the bulk of the tumor that carry drug-resistance mutations and therefore have a survival advantage. Do you think some cancers are more prone to developing drug resistance than others? If so, are there cancer-type specific factors that contribute to this survival advantage? How do you feel precision medicine can overcome the mechanisms of tumor drug resistance?

George M. Yousef: Drug resistance is a major challenge for the majority of metastatic cancer types. There are several reversible and irreversible mechanisms that can contribute to drug resistance. Precision medicine can provide considerable help to delay or even overcome the problem of drug resistance through adjuvant therapy and combination therapy that is based on targeted approaches for the pathways of carcinogenesis and resistance. By crossmatching the genomic characteristics of the tumor with different combinations of therapies, we can develop patient-specific therapeutic combinations to overcome drug resistance. Also, comprehensive genomic analysis of resistant tumors can direct us to other types of targeted therapy based on the genomic status of the resistant tumor.

Gregory J. Tsongalis: One of the hallmarks of human cancer is the continuous replication and thus survival of

the cancer cell. Some cells that are responsive to a drug will acquire new variants that result in the cell becoming resistant to treatment as part of this survival strategy, while other cells are present as a subclone that lingers in the background waiting for an opportunity to proliferate. While the frequency of resistance may vary in certain tumor types vs others, I believe this is a phenomenon that we will face with all tumor types owing to the inherent biology of these cells. As of today, we may not have tools sensitive enough to detect these low level subclones. Radiologically, this is evident in patients with metastatic disease where some nodules are reduced in size and others increase in size in response to the same therapy. We need to do a better job at identifying and treating these subclones in the primary tumor with first line therapy.

As previously mentioned, one strategy to overcome resistance will be the use of combination therapies and development of therapies that inhibit more than one target, such as Sunitinib, a multitargeted tyrosine kinase inhibitor. The use of new, targeted therapies in combination with traditional cytotoxic chemotherapy is showing improved outcomes over traditional therapy alone. Critical to this success is the continued use of a combination of therapies, including chemotherapy, radiotherapy, targeted therapy, small molecule drugs, and immunotherapy. The hope is that the improvement in management strategies afforded by these approaches will result in cancer becoming a chronic disease.

Louis Vermeulen: Intratumor heterogeneity is a great problem for lasting responses to targeted therapies. Indeed, in some cases with spectacular initial efficacy, a resistant subclone emerges that causes a rapid relapse. Interestingly, these subclones often present with similar mutations as those reported to convey resistance in the patient population as a whole. For example *RAS* mutant colon cancers do not benefit from anti-EGFR therapies, and *RAS* wild-type cancers following anti-EGFR therapies frequently display relapses with *RAS* mutant clones. In this respect the mechanisms of resistance both from an intra- as well as inter-tumor heterogeneity perspective, are often similar.

Evidently, cancers that present with a high level of clonal heterogeneity are at higher risk of developing resistant clones following therapeutic pressure. Increasingly sensitive techniques, on biopsy material, or circulating cancer cells or cfDNA, can detect the presence of very small subclones presenting with resistance conveying mutations. In the future, the timely detection of these subclones may guide the use of combination therapies that also target the single drug resistant populations. Alternatively, smarter drug application schemes could be developed that aim to manage tumor evolution and consist of temporary withdrawal of a drug when a resistant clone emerges with the purpose of achieving more long-term disease control. Such "adaptive" therapies, although in their infancy, are very appealing to me.

Ziqiang Zhu: Extensive research has revealed that intratumor genetic heterogeneity contributes to treatment failure due to preexisting subclonal resistance mutations to molecularly targeted agents. Exploring tumor profiling for a better understanding of how tumors develop resistance is essential for successful cancer treatment. Early detection of preexisting drug resistance enables more personalized use of targeted cancer therapy. It also allows us to identify drugs that will serve no benefit and thus avoid unwanted side effects.

On the other hand, resistance to targeted drugs could be acquired from tumor cells via their continuous adaption to selective pressures. For example, the *BRAF* V600E mutation is detected in approximately 50% of melanoma patients. BRAF inhibitor alone often leads to rapid emergence of drug resistance (as a result of the proposed mechanism of paradoxical activation of the MAPK (mitogen-activated protein kinase) pathway, which is essential for tumor cell survival). This finding led to the development of combination therapy with BRAF inhibitor and MEK (mitogen-activated protein kinase kinase) inhibitor by targeting the different molecules in the same signaling pathway. This combination therapy has proven to be effective for delaying the emergence of drug resistance in advanced melanoma.

Suzanne Kamel-Reid: It is likely that some cancers are more prone to developing drug resistance than others, depending on environmental factors and vascularization of the tumor, in addition to the impact of the environment on genetics. Tumors with a higher mutation rate or greater genetic instability, for example, may be prone to developing primary resistance. Acquired resistance may be more likely in some cancer types than others due to the tumor's response to the selection pressure applied by the therapy. Additionally, cancer stem cells, which have different functional properties than the bulk of the tumor, may survive in a genetically altered way to give rise to a new tumor clone post-therapy.

Precision medicine can be used to provide a landscape of the genetic and environmental forces acting on the tumor pre- and post-therapy. However, this requires that tumors be monitored in a temporal and spatial manner, preferably noninvasively (e.g., through analysis of cfDNA). Mutation burden can also be used as a marker of patient response or relapse [e.g., mutation number in the context of immunotherapy for melanoma; mutations present postchemotherapy in the context of AML (acute myeloid leukemia)]. In this way, precision medicine can be used to *identify* mechanisms of tumor resistance, *monitor* their evolution and *suggest* potential treatment ap-

proaches, but not necessarily *overcome* mechanisms of tumor drug resistance.

A major unmet clinical need in cancer research is cancer prevention. What role can precision medicine play in cancer prevention?

George M. Yousef: Precision medicine can play an important role in cancer prediction through screening for cancer risk. This will enable early intervention and prophylactic measures to be taken for better patient outcome. We should be, however, very cautious before adopting cancer screening programs to avoid the problem of over diagnosis and over treatment. Although cancer screening has resulted in a number of success stories in colorectal and cervical cancers, its value in other cancers, including prostate and breast cancers still remains a subject of vibrant debate. Criteria for screening, similar to the World Health Organization–published criteria, should be strictly enforced to ensure success of cancer screening. Other major challenges for the use of genomic profiling approaches for cancer screening are the risk of "incidentaloma" (incidental findings), and the availability of action items to be targeted. Also, false-positive results should be carefully addressed.

Gregory J. Tsongalis: Prophylactic treatment in healthy or asymptomatic patients may not be the best approach for cancer prevention but better surveillance with new biomarkers may be. Precision medicine also impacts population medicine as well as individual medicine. New methods for cancer screening will certainly impact detection, prognosis and outcomes. However, with respect to cancer prevention, we need to address lifestyle and environmental changes.

One potential opportunity in prevention is for routine sequencing of the whole exome or even whole genome. With respect to wellness, this gives the ultimate baseline study for any given individual. However, having said that, a major misconception with respect to oncology is that this information would answer all of the clinical questions we are asking about cancer. That may or may not be true as the variants we seek in tumor cells are somatic and acquired at various time points in the course of the disease. Thus for cancer applications, detecting variants must be cell or tissue sensitive as well as time sensitive.

Another potential big concept for prevention in oncology resides in a better understanding of our immune system and its responses as well as in the understanding of the microbiome, neither of which is a stagnant target.

Louis Vermeulen: The first group of people that come to mind that could benefit from precision medicine in a preventive setting are individuals that present with genetic cancer-predisposing syndromes. The critical feature of these individuals is that the initial driver event of their malignancy is known. In patients with familial adenomatous polyposis (FAP), the initiating event is loss of the single functional *APC* (APC, WNT signaling pathway regulator) gene as the other is already germ line impaired. In heritable retinoblastoma, the same concept applies for the *RB1* (RB transcriptional corepressor 1) gene. It is perceivable that target drugs can be used to limit the outgrowth of these often premalignant clones that occur after loss of the single functional tumor suppressor gene in a cell. Indeed such examples exist and my group recently reported that BCL-2 inhibition specifically induces apoptosis in *APC* deficient cells. Potentially this presents a promising target to limit formation of colon cancer in FAP individuals. In my view, in the future, each cancer predisposing syndrome will be "treated" with syndrome driver mutation-specific preventive interventions.

Ziqiang Zhu: Precision medicine plays critical roles in cancer prevention including risk stratification of cancer screening as well as chemoprevention. Although still very challenging, one of the most important aspects in cancer prevention is using risk stratification strategies for early detection of premalignant lesions and early stage cancers. One way is development and validation of novel biomarkers, especially in patients harboring cancer predisposition genes such as those with high penetrant mutations. Multiple studies have demonstrated the benefit of early screening of such genes.

In terms of cancer chemoprevention, for example, recent studies further revealed mutations in *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) may predict aspirin efficacy in colorectal cancer prevention. Therefore, newer approaches based on precision medicine strategies may change the standard of care of cancer prevention. Eventually, we will have the ability to prevent cancer both at the individual and population level to further promote public health.

Suzanne Kamel-Reid: Precision medicine can play a variety of roles in cancer prevention through analysis of inherited and somatic changes. For example, molecular profiling can be used to identify and monitor genetic markers of susceptibility and predisposition within families through analysis of premalignant lesions, such as leukoplakia in the context of head and neck squamous cell carcinoma, for better risk prognostication and follow-up. In addition, the identification of mutations can help derive a better understanding of the contribution of environmental factors by their type and prevalence. For example, C>T/T>C transitions in the genome are correlated with smoking.

Implementation of precision medicine introduces ethical issues embedded in clinical decisions. Targeted therapies, which are often "last chance" drugs, are extremely costly yet improvement of life expectancy with the majority of these drugs is measureable in only weeks or months. How do you think we should address this issue?

George M. Yousef: It is very important to realize the important fact that "statistical significance" is not always equivalent to "clinical relevance." A number of steps have to be taken to address this important issue, including comprehensive pretreatment counseling with a clear description of the pros and cons of each treatment. The patient should also be aware of the complications, toxicity, and the side effects of the proposed therapy and realistic life expectancy under this particular treatment. Also, transparency in publishing results of clinical trials is needed. In addition, a multidisciplinary committee is needed to develop guidelines for implementation of secondary or tertiary lines of treatment, taking into account cost-effectiveness and toxicity, in addition to quality of life and the health system burden.

Gregory J. Tsongalis: Morally and ethically, this is a difficult issue. Newer therapies typically are approved for use in patients that have failed first, second and sometimes third lines of treatment. We are only now starting to see the introduction of these therapies at an earlier stage in the course of the disease. Accessibility to these therapies, either because of costs or geographic location, is a major issue. Precision medicine has, as its foundation, an understanding of the genomic attributes of the tumor cells that will make them susceptible to therapy. The use of costly or off-label drugs must be approved by payers who may not appreciate the clinical necessity or urgency. However, if we look solely at the cost:benefit ratio, then many would agree that this therapy is not worth it.

At the same time, we expect humans to be immortal or at least for us to try and prolong life for as long as possible. I am not sure that I can morally put a price tag on this and everyone's criteria will be different. Having dealt with the care of 2 elderly parents, I can honestly say that this is not an easy process and the decisions to be made are very difficult. This is an issue that truly tests our morality but we need to deal with and realize the fact that nobody lives forever and our healthcare system cannot sustain such therapies. From the medical perspective, each patient is a resource for scientific and medical information that enhances our understanding of disease, of the therapies used to treat the disease and of our ability to live with disease. As a clinical scientist and human being, trying for anything less is not acceptable but we have to draw the line somewhere and work towards reducing costs of drugs and increasing accessibility to these drugs so that we can provide the best possible patient care.

Louis Vermeulen: This is a huge problem. In my view there are several ways in which we should tackle this. Firstly, increased knowledge will allow us to optimize the selection of patients for specific (combinations of) targeted drugs, which will greatly increase the efficacy, and thereby reduce the costs. Secondly, pharmaceutical companies should be more transparent and report the true costs of drug development and clinical testing. It is a myth that development of a new drug is in the range of a billion US dollars that needs to be earned back before the patent expires. Thirdly, we are very bad in predicting clinical efficacy using preclinical (in vivo) models. This needs to be improved such that ineffective drugs are halted earlier in the development pipeline thereby cutting down total expenditures. And lastly, we need to establish a model in which the financial risks associated with drug development are shared between pharmaceutical industry, academic institutions, governments and healthcare insurance companies.

Ziqiang Zhu: Extending a patient's life only for a few weeks or months may not seem significant, however, we have to keep in mind that these patients are usually extremely sick with no promising treatment options remaining, therefore, they turn to targeted drugs. It is true that in reality, one of the factors that stands in the way of precision medicine becoming more widespread, is the cost.

In theory, targeting the right mutation in the right patient population should offer maximum benefits with decreased side effects, and therefore produce substantial savings and a reduction of costs in the long term. We know that the cost of rapidly sequencing a genome has already significantly fallen to a few thousand dollars. In addition, novel techniques and tools have helped shorten drug development time compared to traditional methods. In fact, several recent studies have revealed that additional survival is not associated with increased costs using targeted therapies. However, there seems to be a lag between the substantial investments in precision cancer therapy and the accumulated data showing significant improvements in health as a result.

Suzanne Kamel-Reid: There are several targeted therapies used as standard of care for patients, often in early stages of their cancers: imatinib in CML; vemurafinib in V600E BRAF melanoma; TKI (tyrosine kinase inhibitor) in EGFR-mutated lung; retinoic acid in APL (acute promyelocytic leukemia). However, targeted therapies are often trialed in the "last chance" setting as a result of the nature of the current clinical trials process. Several

efforts are underway to consider how to improve the likelihood of targeted therapy success by enriching for patients with variants responsive to targeted therapies in trials; however, all of these are still predicated on clinical trials being last resort options. The ideal targeted therapy perhaps ought to be applied to patient care early as opposed to late, and trialed in that context as well. Current newer trial approaches such as "basket" trials incorporate precision medicine into the trial design and are based on the hypothesis that the presence of a molecular marker predicts drug response, regardless of tumor histology. Approaches such as these will increase our ability to identify favorable responses even in small patient cohorts and may identify long-term effects.

What would you like to see in the future of precision medicine for oncology?

George M. Yousef: I believe that we are approaching a new era of precision medicine in oncology, which will have significant impact in improving patient outcome. It is important to remember that precision medicine is not likely to provide a "once and for all" solution for most oncology problems. A targeted approach, which focuses on specific well-defined issues where actionable items are available, is needed. Also, guidelines and regulations should be implemented to control the exponentially growing market of "direct to consumer testing." Thorough pre- and post-testing counseling for genomic testing should be implemented. As much as I am enthusiastic about approaching P4 medicine (a proactive discipline of medicine that is predictive, personalized, preventive, and participatory), with active patient participation in treatment decisions, we should also make sure our patients have the ability to make "informed decisions" to avoid overselling the precision medicine in oncology, especially in the near future.

Gregory J. Tsongalis: I think we need to reconsider the types of testing we are doing. There is clearly room for more meaningful testing and interpretation of results to determine which variants and profiles are most clinically significant. The vast amounts of data being generated by laboratories around the world need to be analyzed in a way that can derive answers to the toughest clinical questions. For example, for one institution to sequence 1000 tumors is quite feasible and that dataset would most likely show that while some variants may be common across tumors tested, no 2 tumors would have the same identical set of variants. As we develop a better understanding of these key points, I think we will be able to come up with better surrogate biomarkers. I am a big fan of microRNA (miRNA) analysis as I think this has been way underutilized by the clinical laboratory community. miRNA analysis could identify genes that are up- or down-regulated in tumor cells whose products could then be tested for by other proteomic technologies. I am very excited about the potential for the liquid biopsy for monitoring disease. We have yet to have such an application with a laboratory test for solid tumors. Finally, I think all of this will lead to more efficacious combination therapies so that cancer can become a chronic disease.

Louis Vermeulen: The future of precision medicine in oncology lies in prevention strategies, starting with the development of familial cancer syndrome–specific preventive agents. The next step is the development of strategies to limit outgrowth of premalignant clones in the entire population that typically only harbor a few oncogenic events and are therefore optimally amenable to targeted interventions.

In the future, for cases with extensive clonal heterogeneity, we will need to develop therapeutic applications that can be adapted as the tumor evolves and acquires mutations over time. In this respect, it is critical that at the start of treatment, comprehensive molecular profiles are obtained thus integrating genetic, epigenetic, tissue of origin and microenvironmental influences, and that these features determine selection of drugs. Subsequently, the effects of drugs need to be carefully monitored by regular peripheral sampling of cfDNA or cells, to assess the changes in clonal composition of the cancer. This has the potential to spot emergence of resistant clones and adapt the therapy before clonal sweeps, after which no effective therapies are available.

Ziqiang Zhu: I believe precision medicine is the future of medicine and especially the future of oncology. Over the next few years, further understanding of the molecular basis of cancer development and the interaction with the immune system will provide more effective therapies with fewer side effects than traditional treatment. Eventually, precision cancer therapy will enable us to offer individualized treatments, and change medical care, patient outcomes and quality of life.

Precision immunotherapy is one type of precision medicine that aims to create a profile of a patient's immune system to fight cancer. We now have a better understanding of how our immune system helps to combat cancer. Checkpoint inhibitor therapies, CARs (chimeric antigen receptors), and adoptive T-cell therapy have been proven to offer a durable response and even eradicate cancer compared to other therapies. However, these powerful therapies only work in a small percentage of patients. Therefore, there is an urgent need to understand the factors affecting response to cancer immunotherapy. In addition, developing novel biomarkers to select patient populations and predict treatment response of immunotherapy is also critical.

Effective multidisciplinary collaboration, especially involving molecular targeted therapy and system immunotherapy will change the paradigm of how we approach cancer treatment to pursue the cure for majority of cancer types.

Suzanne Kamel-Reid: A "wish list" of possibilities includes: more noninvasive methods of molecular profiling; application of integrated molecular approaches ("multiomics," e.g., transcriptional signatures with mutation analysis; copy number, translocation and mutational analysis; methylation, expression and mutational analyses combined) where appropriate and necessary; availability of more drugs targeting more genes and pathways altered in cancers; a better understanding of the underlying biological differences in responders and nonresponders; community definitions of interpretation standards for somatic variants; a better understanding of N of 1 patient management scenarios/successes; more concerted global profiling efforts; and, increased knowledge sharing. Most importantly, I would like to see more affordable and effective medicine for all achieved through efforts in precision medicine.

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