

Application of Cancer Genomics to Solve Unmet Clinical Needs

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The large amount of data on cancer genome research has contributed to our understanding of cancer biology. Indeed, the genomics approach has a strong advantage for analyzing multi-factorial and complicated problems, such as cancer. It is time to think about the actual usage of cancer genomics in the clinical field. The clinical cancer field has lots of unmet needs in the management of cancer patients, which has been defined in the pre-genomic era. Unmet clinical needs are not well known to bioinformaticians and even non-clinician cancer scientists. A personalized approach in the clinical field will bring potential additional challenges to cancer genomics, because most data to now have been population-based rather than individual-based. We can maximize the use of cancer genomics in the clinical field if cancer scientists, bioinformaticians, and clinicians think and work together in solving unmet clinical needs. In this review, we present one imaginary case of a cancer patient, with which we can think about unmet clinical needs to solve with cancer genomics in the diagnosis, prediction of prognosis, monitoring the status of cancer, and personalized treatment decision.

Keywords: drug therapy, early detection of cancer, genomics, health services needs and demand, high-throughput nucleotide sequencing

Introduction

Despite the explosive increase in cancer genomics data, the actual application of genomics data and approach to clinics offers big challenges [1, 2]. The main reason for the delay in the application to clinics is non-connectivity between bioinformaticians, non-clinical scientists, and clinicians. Clinicians are not confident in how much additional information might be given through genomics technology compared to conventional tools, and non-clinical scientists and bioinformaticians are not aware of what clinical problems should be solved with priority.

Cancer clinicians expect novel diagnostic, prognostic, and therapeutic values of this new technology [1]. Now, the clinical field is aware that multiple assays using next-generation sequencing (NGS) has some advantage over single genetic tests [1, 3]. A recent cancer guideline from the National Comprehensive Cancer Network (NCCN) pointed out that epidermal growth factor receptor (EGFR) and/or

anaplastic lymphoma kinase (ALK) testing should be conducted as part of multiplex/NGS in non-small-cell lung cancer (NSCLC) [4].

The feasibility of an NGS diagnostic platform at cancer clinics was validated by cancer centers in the United States [5] and Europe [6]. One platform showed that potential hurdles, time, cost, purity, and ethical problems could be overcome in implementing NGS using low-coverage whole-genome sequencing, whole-exome sequencing (WES), and whole-transcriptome sequencing [5]. Another platform sequenced clinical samples, including formalin-fixed, paraffin-embedded ones, and showed that this approach is practical and can give some benefits to the patients with lung cancer [6].

The WES approach in Mendelian disorders showed that ~25% of sequencing can give a specific diagnosis based on the germline genetic make-up from the data of 250 probands, mostly consisting of neurological phenotypes in real practice [7].

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The clinical application of cancer genomics should be considered in the context of unmet clinical needs to maximize the value of this novel paradigm. Here, we dealt with the potential clinical application of cancer genomics in the aspect of practical management of cancer patients, along with a clinical scenario covering the whole course of cancer management. We overviewed the potential of cancer genomics in the context of real cancer practice through this approach.

Application of Cancer Genomics for Diagnosis

A 64-year-old male presented with a cough since 2 months ago. He quit smoking 10 years ago and had smoked an average of one pack per day for 30 years. He had regular check-ups every year and had the last check-up with no abnormality 6 months ago. His chest roentgenogram showed a mass shadow in the lung. He got a percutaneous needle aspiration (PCNA) and biopsy but did not have any tumor cells. He repeated the PCNA and biopsy but developed pneumothorax (air leakage from lung) related to the diagnostic procedure. His second biopsy showed some malignant cells, suggestive of adenocarcinoma. After a staging work-up with a computed tomography (CT) scan, positron-emission tomography (PET) scan, brain magnetic resonance imaging scan, and bronchoscopy, his tumor was revealed as T2N0 clinical stage. He got a surgery based on the result of the pathology and staging work-up.

In this situation, we face unmet clinical needs of early cancer diagnosis. He was diagnosed with symptoms related to the cancer, despite his regular check-up. If we detect his malignancy before the symptoms, we can get a better result compared with the symptomatic case [8]. This imaginary patient was diagnosed with operable cancer, but as many as 60% to 70% of lung cancer patients are diagnosed with inoperable, advanced disease [9]. To diagnose the cancer sooner, screening procedures have been studied extensively in the clinical field. Lots of trials failed to show an actual benefit of screening strategy in lung cancer [10, 11], but recently, a screening trial using low-dose chest CT of lung cancer was proven to be successful [8]. Low-dose chest CT reduced the mortality from lung cancer through early detection in people with a history of at least 30 pack-years of smoking. Despite this good approach to detect early lung cancer, the reduction of mortality is 20% [8]. This advantage should be counterbalanced with the potential harmful effects of radiation exposure or false positivity [12].

One important usage of genomics should be early detection. Many biomarkers were investigated for the early detection of lung cancer—for example, circulating tumor DNA and RNA [13]. But, false positivity and false negativity of single tests prevent these tests from clinical usage. If we

use multiple biomarkers using cancer genomics for the detection of early cancer, the false positives and negatives could be reduced to the level of clinical usage.

Another effective approach of early diagnosis of cancer is to select a high-risk population for screening tests. Many genome-wide association studies identified some germline single-nucleotide polymorphism (SNPs) that are associated with the risk of cancers [14-16], and these findings suggested important potential germline markers for the definition of high-risk populations. Dr. Mardis told the case of Mike Snyder as an example of an actual application of a germline genome test [17]. He sequenced his own genome and found a higher risk of type 2 diabetes; since that time, he checked his glucose level regularly, and he detected high glucose levels at the very beginning. After that, he exercised regularly and returned to normal glucose levels. The concept of early diagnosis, like the story of Mike Snyder, can be applied to the early detection of cancer, too. If we define a high-risk population with germline genetic tests, we could focus on the use of screening tests in this population. This approach will also save money on screening tests for the whole population.

This patient had a bad experience of pneumothorax. This complication gives pain and discomfort of the sensation of dyspnea, prolongs the period of admission, and increases the cost of cancer management. This problem originated from the invasive nature of the diagnostic procedure—PCNA and biopsy using a needle, moving back and forth through the patient's fragile lung tissue. New diagnostic tools using cancer genomics—for example, identification of cancer-specific genetic alterations from circulating tumor DNA—can avoid this type of complication from invasive procedures. One pioneering study showed that circulating tumor DNA could be combined with genomic technology to diagnose and monitor the status of cancer very safely [18].

Application of Cancer Genomics for Prognosis

He underwent surgery performed by thoracic surgeons. His final pathological diagnosis was adenocarcinoma and revealed the involvement of some mediastinal lymph nodes; therefore, the final pathological stage was T2N2, IIIA. This stage required adjuvant chemotherapy, and he was referred to the department of medical oncology. A medical oncologist prescribed adjuvant chemotherapy—a navelbine and cisplatin regimen (NP) for 4 cycles.

NP 4 cycles has been prescribed to patients with high-risk clinical stage IB, IIA, IIB, IIIA, and IIIB, regardless of other clinicopathological factors. The actual benefit from this treatment is only a 4% long-term survival advantage, with some hematological and non-hematological toxicities [19,

20]. The way to improve the risk-to-benefit ratio of adjuvant treatment is further selection of a patient population that could benefit from this treatment. Stage-based risk calculation – the current practice – cannot predict an accurate risk of relapse and attenuates the value of adjuvant treatment. Single patient-based risk calculation should be done to identify the adequate patients for adjuvant treatment. Cancer genomics will provide useful tools for a single patient-based risk calculation model. This personalized adjuvant model will definitely increase the proportion of patients who benefit from it.

There are also clinical needs of prognosis prediction even before surgery. Surgical management of stage IIIA is controversial. If he had been diagnosed as stage IIIA preoperatively, he might have chosen a no-surgery option, such as concurrent chemoradiation, because no definite benefit of surgery was demonstrated until now, although this is controversial [21, 22]. We have relatively sensitive diagnostic methods, such as CT, PET, and endobronchial ultrasonography, but the sensitivity and specificity are still not perfect. One focus of genomics technology should be a more accurate prognosis preoperatively, in addition to post-operatively.

Prediction issues in cancer patients are not limited to survival, recurrence, and response to specific treatment. The goal of cancer care is improvement of survival and, more importantly, quality of life. Predictive markers of bone metastasis or bone-related events, such as fracture or paralysis, are very important to improve the quality of life in cancer patients. We have no clinically validated markers to predict these events [23]. An unbiased approach is needed to discover good biomarker for these events, because we have very limited clues to dig into these problems. The most important advantage of genomics approach is that is “unbiased” with regard to any hypotheses or theories. That is why clinical problems with low-depth knowledge are a good candidate for the application of cancer genomics. The connection between clinicians and genomic scientists can facilitate the development of clinical problems that are solved with a genomic approach.

Application of Cancer Genomics for Monitoring

He got 4 cycles of adjuvant chemotherapy and then followed up regularly with a physical examination, blood test, CT scan, and/or PET scan. At 6 months since the completion of adjuvant chemotherapy, he presented with right-side chest pain, and his CT scan showed tumor relapse in the right lung and pleura. He planned systemic anticancer treatment for life prolongation and palliation of symptom, not curative.

The role of CT scan and/or PET scan is not defined [24], but many clinicians use this high-cost image for monitoring relapse. The reason for the popular use of this high-cost image is that there is no other alternative of monitoring cancer status. Recent studies showed the possibility of circulating tumor cell and cell-free DNA as a tool for monitoring tumor status [18, 25]. Cancer genomics enables circulating tumor cell or cell-free DNA to detect relapse earlier than image findings or tumor markers. The delicate delineation of circulating DNA with NGS technologies is an essential part of this success story. No tool is available with a definite clinical benefit for the monitoring of cancer; therefore, we absolutely need new, non-invasive tools for it. Because it takes at least several years to prove the benefit of monitoring, we should start a well-designed prospective study using cancer genomics to prove it as soon as possible.

Application of Cancer Genomics for Therapeutics

The medical oncologist who was in charge of him tested for EGFR mutation and ALK by fluorescence in situ hybridization to see rearrangements of ALK. Tests showed no EGFR mutation and no ALK translocation. He chose cytotoxic chemotherapy with pemetrexed and cisplatin according to the double-negative results of the EGFR and ALK tests.

The ultimate goal of the clinical application of cancer genomics should be therapeutics. There are increasing gene lists for NSCLC that have matching targeted agents [26, 27], but many patients do not have genetic alterations that can be a target. Even for the same type of cancer – for example, lung adenocarcinoma – the genetic make-up is very heterogeneous. The accurate definition of the genetic make-up of each patient will be the first step for personalized medicine. Many target panels have been developed by many vendors and hospitals for commercial or non-commercial use [3], but the usage is still very limited. As more cancer genome data are available [28, 29], the list of target panels will increase and be specified to tumor types.

Now, we have two targeted agents to prolong the survival of lung cancer patients: the EGFR tyrosine kinase inhibitor (TKI) erlotinib or gefitinib for EGFR mutations and the ALK TKI crizotinib for ALK translocations. For this case, there was no targeted agent, because he did not have EGFR or ALK alterations. Based on the histology of his tumor, he was treated with pemetrexed and cisplatin [30]. Despite the substantial toxicity of cytotoxic chemotherapy, many patients are prescribed these drugs with the individualized possibility of this agent not known. This decision relies on population data from large-scale prospective trials. Because clinical trials targeting specific genetic alterations are increa-

sing, the clinical need for more genetic information is also increasing [31].

If the patient was diagnosed as stage IV initially, the amount of tissue for genetic testing is very limited. The amount of tissue is enough for 2 or 3 genetic tests. For these patients, multiplexing or NGS technologies have important advantages to overcome the limitation of tissue amounts in the clinic.

This patient got adjuvant chemotherapy with NP for 4 cycles but progressed 6 months after the completion. We guess that the patient did not benefit from NP for 4 cycles. The usual speculation is whether there is a better way to choose adjuvant treatment. The way to increase the benefit of adjuvant treatment could be the application of variable adjuvant treatment that is selected from individualized factors. Personalized cancer genomic analysis can show different and private profiles of individual cancers, and accumulation of these genomic data enables different adjuvant treatment strategies for each patient.

Despite the theoretical promise of personalized cancer genomic analysis for the selection of the right drug, there are few examples of this direct application of cancer genomics. One of important example is the story of Lukas Wartman, a doctor at Washington University in St. Louis [32]. He suffered from a second relapse of acute lymphoblastic leukemia and sequenced the tumor DNA and RNA. He found very high expression of FLT3 and then figured out that sunitinib, a kidney cancer drug, could block tumor survival signals. Sunitinib induced complete remission in him, and thereafter, he received allogeneic stem cell transplantation and is now in remission. Another story from the Fox Chase Cancer Center was reported on *KIT* mutations from a pancreatic neuroendocrine tumor [33]. The patient had an advanced pancreatic neuroendocrine tumor and sequenced his tumor using a cancer panel. He had a *KIT* mutation and was treated with imatinib, a well-known *KIT* inhibitor that is not approved for his tumor, for more than 2 years. If he had been in in routine practice without cancer panel sequencing, he would have died without imatinib treatment.

A pharmacogenomic approach could be used to minimize toxicity to cancer treatment, too. In this case, we usually see germline SNP data. Some germline SNPs are already known to predict erratic side effects to specific drugs. One example is the *UGT1A1* germline polymorphism for the metabolism and toxicity of irinotecan. If the patient has a homozygous polymorphism in the *UGT1A1* gene—the *28 variant—he should be prescribed with a dose reduction to avoid severe, sometimes fatal, toxicity from irinotecan. A genomic approach is required to properly assess pharmacogenomics in association with drug toxicity. A commercial chip, the Affymetric DMET chip, covers 25–32% of genes of phar-

macogenomics, and it is an important question whether more coverage with WES will be more beneficial.

He was treated with pemetrexed and cisplatin for 4 cycles, and his tumor shrank with the treatment. But, his tumor rebounded, with a complaint of dyspnea and cough, 4 months after the completion of treatment. After 4 cycles of second-line chemotherapy with docetaxel, he had stable disease.

Even in the case of a dramatic response to the first-line treatment, nearly all cancers rebound with various relapse-free durations [30, 34]. The choice of second-line treatment depends on clinical guidelines, clinical parameters, and clinicians' experiences. Any of the parameters may not be best if a specific patient's situation is not considered. We do not know the exact mechanism of resistance to the previous treatment and do not have any good way to assess the mechanism of resistance. If cancer genomics is adopted in this situation, we can profile the tumor tissue that was resistant to the previous treatment. The profile can help clinicians decide on a second-line treatment option and improve the individual's outcome. The resistance mechanism could vary, depending on multidimensional factors, such as the patient, tumor biology, and previous treatment. Especially, this situation should be approached individually with the concept of true personalized medicine.

*His disease began to grow again and he refused further cytotoxic chemotherapy. He was in hospice care and died 1 year after the initial diagnosis of relapse. After his death, his tumor was sequenced by whole-transcriptome analysis, and his tumor showed a *ROS1* translocation. Now, a *ROS1* inhibitor is available for this type of cancer.*

The median overall survival of metastatic lung cancer patients is 1 year if there is no genetic alteration for which targeted agents are available [30, 34], as in this case. If the patient has an *EGFR*-sensitive mutation or *ALK* translocation, the median overall survival time reaches 2 years [35, 36]. A *ROS1* targeting agent, another example of successful targeting of oncogene addiction, is now available after his death [27]. If the *ROS1* translocation was known for his tumor and he was treated with a *ROS1* inhibitor, he could have a chance to live an additional one year or more. Tumors have very heterogeneous profiles [37, 38], and resistant tumors have even more heterogeneous ones [39]. This is why tumors should ultimately be approached on an individual basis, rather than a population basis.

Conclusion

Now is the right time to think about how we can use cancer genomics for individual patients. There are still lots of technological hurdles—e.g., functional annotation of sequencing results, the way to integrate multi-dimensional

data, and the exploration of the clinical meaning of sequencing variants for the routine clinical usage of cancer genomics. Defining unmet clinical needs is as important as overcoming technological hurdles to maximize the benefit from cancer genomics. Early detection, non-invasive molecular diagnosis, risk prediction of relapse and tumor-related events, monitoring of disease status, matching good drugs, and finding out personal grade resistance mechanisms are good examples of unmet clinical needs that should be solved with cancer genomics. It would speed up and optimize the application of genomics to cancer clinics if cancer biologists, bioinformaticians, and cancer clinicians cooperate towards one goal of achieving it.

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