Molecular Profiling and the Reclassification of Cancer: Divide and Conquer

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OVERVIEW

Cancer is one of the leading causes of mortality in the world. Choosing the best treatment is dependent on making the right diagnosis. The diagnostic process has been based on light microscopy and the identification of the organ of tumor origin. Yet we now know that cancer is driven by molecular processes, and that these do not necessarily segregate by organ of origin. Fortunately, revolutionary changes in technology have enabled rapid genomic profiling. It is now apparent that neoplasms classified uniformly (e.g., non-small cell lung cancer) are actually comprised of up to 100 different molecular entities. For instance, tumors bearing ALK alterations make up about 4% of non-small cell lung cancers, and tumors bearing epidermal growth factor receptor (EGFR) mutations, approximately 5% to 10%. Importantly, matching patients to therapies targeted against their driver molecular aberrations has resulted in remarkable response rates. There is now a wealth of evidence supporting a divide-and-conquer strategy. Herein, we provide a concise primer on the current state-of-the-art of molecular profiling in the cancer clinic.

MOLECULAR TECHNOLOGY OVERVIEW

Morphologically, many tumors look alike, even though they may be vastly different at the molecular level. Cytogenetic studies do reveal a multitude of chromosomal abnormalities across malignancies; nevertheless, technicalities such as the amount of tissue required, need for dividing cells, and lack of sensitivity attenuate their contribution to diagnostics. Molecular studies are often both sensitive and specific, and can detect aberrations in samples with low numbers of malignant cells. They can also be used to discern minimal residual disease and improve molecular staging (e.g., more stringent monitoring of a low-burden morphologic tumor with high-risk molecular stratification for recurrence). Just as cytogenetic techniques improved over time from basic karyotyping by band analysis to fluorescence in situ hybridization (FISH) and subsequently to comparative genomic hybridization (CGH), molecular evaluation has also come of age. Molecular diagnostics is an ever-growing field and its techniques involve polymerase chain reaction (PCR), mass spectrometry, amplification refractory mutation system (ARMS), genotyping microarrays, oligonucleotide hybridization, direct sequencing of the genome using next-generation sequencing (NGS) technology, transcriptome sequencing, and proteomics. Fast-paced technologic improvements will continue to decrease the turn-around times and the cost of these
methods. An avalanche of data growing in complexity will soon follow, and the appropriate use of such information for diagnostic and prognostic classification will be the true foreseeable challenge in the years to come.

MOLECULAR PROFILING: A BRIEF HISTORY

In the 1980s and early 1990s, it was common to hear the conventional wisdom that the human genome, because of its complexity, would “never” be sequenced. Yet the Human Genome Project, which was started around 1990, was declared complete in April 2003, with an initial rough draft of the human genome available in June 2000.4,5 The project cost over $3 billion. In subsequent years, technology has advanced at lightning speed. Today, genomic sequencing can be performed in a matter of days for $1,000 to $5,000 dollars. However, the immense datasets generated still present a challenge from a bioinformatics standpoint. As a result, usable clinical information in the oncology field is often derived from tests that examine a subset of genes (usually anywhere from 40 to about 230). A variety of techniques are employed, including those that utilize next-generation deep sequencing or, alternatively, hot spot mutation assessment, as well as others. Finally, though we have entered an era in which the cost of clinical-grade whole-genome and exomic sequencing is no longer prohibitive, the infrastructure to support the patient and physician has not fully kept pace.

SELECTED TYPES OF MOLECULAR PROFILING

Next-Generation Sequencing

Next-generation sequencing (NGS) represents a new technology with a unique approach to sequencing entire genomes which has already spurred numerous ground-breaking discoveries and triggered a transformation in genomic medicine. The DNA is first fragmented into a library of small segments that can be uniformly and accurately sequenced in millions of parallel reactions. The newly identified strings of bases, known as reads, are then reassembled using a known reference genome as a scaffold (resequencing), or in the absence of a reference genome (de novo sequencing). The full set of aligned reads identifies the complete sequence of each chromosome in the DNA sample.

Several human genomes can now be sequenced in roughly one week, for a reagent cost of less than $5,000 per genome. As mentioned above, in comparison, the first human genome required over a decade to sequence and came with a price tag of $3 billion.

Although the latest high-throughput sequencing instruments are capable of massive data output, NGS technology is highly scalable. The same underlying chemistry can be exploited for targeted gene analysis that is currently applicable to routine use in the clinical setting.

Exome Sequencing

Exome sequencing is an efficient strategy to selectively sequence the coding regions of the genome as a cheaper but still effective alternative to whole genome sequencing. Exons are short, functionally important sequences of DNA that represent the regions in genes that are translated into protein. Exome sequencing is, however, only able to identify those variants found in the coding region of genes that affect protein function. Approximately 99% of the human genome is not covered using exome sequencing. Hence, exonic sequencing is not able to identify the structural and noncoding variants associated with a disease; the identification of these noncoding variants requires whole genome sequencing.

Whole Genome Sequencing

Whole genome sequencing is a process that determines the complete DNA sequence. This process entails sequencing all of the chromosomal DNA as well as DNA contained in the mitochondria. A number of public and private companies are competing to develop a full genome sequencing platform that is commercially robust enough for both research and clinical use.

DNA Mass-Arrays

Mass-arrays can be used for single nucleotide polymorphisms (SNP) genotyping, methylation detection and quantitative gene expression analysis, and copy number determination. Many DNA mass-arrays offer 10 to 60 gene panels with quick turn-around times suitable for use in oncology.6

Comparative Genomic Hybridization (CGH)

CGH is also known as chromosomal microarray analysis. It is a powerful technique to detect gene copy number variations and structural alterations, including but not limited to micro-deletions.

Transcriptomics

Whole transcriptome sequencing, also known as RNA-seq, refers to the use of high-throughput sequencing technologies to sequence cDNA (derived from RNA) in order to obtain information about a sample’s RNA content. With deep coverage and base-level resolution, next-generation sequencing of cDNA derived from RNA provides information on differential expression of genes, including differential allelic expression and differently spliced transcripts.
cies such as the U.S. Food and Drug Administration (FDA) regulated demand for individualized products. Regulatory agencies, even in the research setting, must meet criteria embodied against putative sites of activation (phosphorylation) on protein analyses and the evaluation of their cellular compartmentalization.

Metabolomics
The metabolome represents the collection of metabolites in a biologic tissue, which are the end products of cellular processes. Integrating metabolomics data with genomic, transcriptomic, and proteomic information can provide a more complete picture of the functional signature of a cell or organism.

SELECTED CLINICALLY RELEVANT PROCESSES AND DESIGNATIONS
Clinical Laboratory Improvement Amendments (CLIA)
In the United States, laboratory tests run for patient care purposes, even in the research setting, must meet criteria embodied in the Clinical Laboratory Improvement Amendments (CLIA) of 1988. This legislation standardized quality assurance practices in clinical labs, and required them to measure performance at each step of the testing process from the beginning to the endpoint. CLIA is not required in countries outside the United States. It is a matter of debate whether or not the requirement for CLIA in the research setting has slowed introduction of new molecular technologies for use in clinical trials.

Companion Diagnostics
The dawn of personalized medicine has produced an associated demand for individualized products. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) are mandating that, with the new generation of targeted drugs, pharmaceutical companies identify the subpopulation of patients who harbor the molecular target affected by a novel agent. A companion diagnostic generally focuses on a single aberration that would be used to select patients for the targeted agent being developed. Stringent criteria are utilized to evaluate the accuracy and usefulness of the companion diagnostic. Companion diagnostics have permitted the selection of subsets of patients who are more likely to have a disease response, and hence brought drugs to market that might otherwise have been abandoned. An excellent example is trastuzumab, which has salutary effects in only a subgroup of individuals with breast cancer, and might never have been approved had the test for HER2/neu not been developed.

Although initially a progressive concept, the rapid evolution of technology has revealed basic flaws in the companion diagnostic idea. Most importantly, if a disease such as breast cancer is composed of 100 molecular subsets, it is impossible for a physician to know a priori which companion diagnostic to utilize. Testing with multiple companion diagnostics would be exorbitantly expensive and would require large amounts of tissue. Most importantly, with the advent of multisess assay platforms for molecular profiling, patients can be tested for hundreds or even thousands of genes at the time of referral, making the companion diagnostic redundant.

Bioinformatics
The statistical analysis of the enormous quantity of data generated from modern sequencing approaches is a challenge. Even low rates of false-positive or negative findings are also a crucial issue. Today, bioinformatics processing, not technical sequencing capacity, is the rate-limiting step in our ability to exploit genomic datasets. Because of bioinformatic limitations, data derived from subsets of genes, usually about 50 to 250, is more likely to be usable in real time in the clinic than data derived from whole genome sequencing. It is anticipated that a leap in bioinformatics capability will occur soon, and the landscape will once again shift in this regard.

MOLECULAR HETEROGENEITY
The Vogelstein model of stepwise progression of cancer evolution, from normal epithelium to adenoma to carcinoma to metastasis, was described in 1990. The road from normal cells to cancer cells, through an intermediary (i.e., polyp) was depicted in colon cancer, perhaps because of the relatively ease of access to tissue sampling thanks to endoscopic screening surveillance. APC gene mutations may occur earlier in colon cancer, whereas p53 suppressor gene mutations may occur later. Supporting this theory, polyp removal via colonoscopy demonstrated in clinical trials its capacity to decrease the incidence of colon cancer. More recently, the adenoma/carcinoma stepwise approach (initiation, promotion, progression) has been complemented by the theory of branched evolution. A possible nonlinear biologic evolution
of some tumors may be represented by a dynamic malignant process of de-differentiation/redifferentiation.

Knudson’s “two hit” hypothesis explained how either sporadic or hereditary childhood retinoblastoma could be secondary to a mutated retinoblastoma (RB1) gene in a two-step fashion (a first germ-line mutation followed by a second somatic mutation, or two somatic mutations). Other models of pathogenesis do, however, exist. For instance, Helicobacter pylori can be the triggering event leading to a chronically inflamed gastric epithelium, which in turn leads to intestinal metaplasia and then to dysplasia and carcinoma. Regression of gastric precancerous lesions has been seen after antibacterial therapy directed against Helicobacter pylori. On the other hand, molecular “hits” in gastric cancer may include oncogenes (KRAS, c-met), tumor suppressor genes (TP53, TP73, APC, TFF, FHIT, DCC or deleted in colon cancer), cell cycle regulators (Cyclin E) and epigenetic events (DNA methylation of genetic promoters silencing certain genes). Finally, it has been suggested that abnormalities in the tumor microenvironment, in concert with actual tumor aberrations, also contribute to malignant progression.

Recent studies show that molecular evaluation of metastatic disease by a repeat biopsy performed on progression might unveil a different genetic makeup than the initial biopsy obtained on the original diagnosis. Furthermore, heterogeneity in metastatic disease exists between tumors and even within single tumors. Many tumors at the time of relapse have numerous molecular aberrations. It is now apparent that there are multiple pathways that can lead to a single type of cancer and, further, as tumors evolve, a multitude of new aberrations develop even within individual tumors.

**GENE PROFILING IN BREAST CANCER**

Breast cancer was one of the first solid malignancies in which the use of molecular signatures to stratify patients was adopted. Tests for HER2/neu in breast cancer are not only prognostic but also allowed physicians to choose the optimal adjuvant or palliative targeted therapy for this population of patients. Clinical calculators have been used in this regard as well (i.e., Adjuvant! Online). Molecular profiling in breast cancer based on age, node status, tumor size, and tumor grade.

It is now recognized that the heterogeneous group of breast cancers is not one disease, but many. Molecular analysis is further characterizing breast cancer by gene expression profile into several intrinsic subtypes based on gene clustering. Indeed, invasive breast cancers can be classified by gene expression profiling into four major biologic subtypes referred to as Luminal A, Luminal B, HER2-enriched, and Basal-like. These subtypes have been identified using several technologies including microarray, immunohistochemistry, and reverse-transcriptase polymerase chain reaction (RT-qPCR). Other subtypes such as basal-like, claudin-low, interferon-rich, and androgen receptor–positive have been described, and it is probable that yet more subtypes will be identified over time.

**Oncotype DX**

A 21-gene recurrence score assay is often used for patients with breast cancer. From the approximately 25,000 genes in the human genome, 250 candidate genes possibly associated with breast cancer tumor behavior were identified. These genes were analyzed in several hundred patients in clinical studies in order to identify a panel of 21 genes strongly correlated with distant recurrence-free survival. The panel consists of 16 cancer genes and five reference genes used to normalize the expression of the cancer genes. The Oncotype DX test is now established as a diagnostic test that helps identify which women with early-stage, estrogen receptor–positive, and lymph node–negative breast cancer are more likely to benefit from adding chemotherapy to their hormone treatment. This test also assesses the likelihood that an individual woman’s breast cancer will relapse. Postmenopausal women recently diagnosed with node-positive, hormone receptor–positive breast cancer may also be appropriate candidates for the test. For prognostication, the test provides a Recurrence Score, which is a number between 0 and 100 that corresponds to a specific likelihood of breast cancer recurrence within 10 years of the initial diagnosis, with buckets of Low, Intermediate, or High Risk.

**MammaPrint**

MammaPrint is a diagnostic test to assess the risk that a breast tumor will metastasize and helps physicians decide whether or not a patient will benefit from chemotherapy. It is based on the Amsterdam 70-gene breast cancer gene signature. It uses fresh tissue for the microarray analysis. The test analyzes these 70 genes to see how active they are and then calculates either a high-risk or a low-risk recurrence score. It has been examined extensively for patients of all ages with breast cancer who are lymph node–negative, regardless of estrogen receptor (ER) status, with tumors of less than 5 cm.

**Mammostrat**

The Mammostrat test is used to estimate a woman’s risk of recurrence of early-stage, hormone receptor–positive breast cancer. It measures the levels of five genes in breast cancer cells. These measurements are used to calculate a risk index score. The higher the risk index, the higher the risk of relapse. Women are assigned to a stratified risk category (high, moderate, or low) based on their risk index score.

**Other Tests**

PAM50, which as the name implies evaluates 50 genes, and the Rotterdam/Veridex 76-gene test are currently under evaluation. Technically, these molecular portraits in general are based on arrays measuring expression of a cluster of genes via assessing mRNA that binds to specific genetic probes in an array and by comparing levels in the actual tumor with normal reference tissue. The concomitant analysis of countless patterns of expression of genes ultimately narrows the search to a more defined number of candidate genes, perhaps less than a hundred, identifying a molecular signature in a particular type of tumor which will disclose its inherent biologic
properties and/or its correlation to clinical endpoints. A plethora of other multigene assays are under development. In addition, individualized genome-wide molecular tumor analysis, with platforms as FoundationOne, Caris Target Now, and SNaPshot, provide additional tests that can bring the possibility of personalized medicine to patients.

LUNG CANCER: DIVIDE AND CONQUER EXEMPLIFIED

Cytotoxic chemotherapy has recently found a contending challenger in metastatic non–small cell lung cancer (NSCLC) as our understanding of the molecular drivers of disease led to the development of targeted agents directed against mutations in the epidermal growth factor receptor (EGFR) predicting response to erlotinib\(^1\) and rearrangements of the anaplastic lymphoma kinase (ALK) gene predicting response to crizotinib.\(^1\) The latter drug is also active in patients with ROS1 translocation.\(^1\) A slate of other candidate mutations (Fig. 2) are being paired with drugs (RAS mutations with MEK inhibitors\(^2\); PIK3CA or PTEN mutations with PI3kinase, AKT, or mTor inhibitors\(^2\); RET translocations with RET inhibitors,\(^2\) HER2 mutations with HER2 antibodies or inhibitors,\(^2\) and MET aberrations with MET kinase inhibitors). Not surprisingly, however, most tumors develop resistance and disease relapses, probably because these tumors harbor multiple aberrant molecular drivers. Therefore, long-term disease control will require combination therapies tailored to individual patients, and/or moving treatment to an earlier stage of disease.

SOLID TUMORS: LEARNING FROM THEIR HEMATOLOGIC COUNTERPARTS AND VICE VERSA

Genetic mutations can be inherited (familial cancer from germ-line mutations) or acquired (sporadic cancer from somatic mutations). To add another layer of complexity to molecular analysis, other carcinogenic drivers include gene deletion, amplification/overexpression, gene rearrangement, and DNA methylation. From a Darwinian standpoint, if these abnormal tumor cells carry a growth advantage then it may result in clonal evolution and expansion of the fittest; nevertheless not all genetic events may result in clonal evolution as some will be neutral and some will be detrimental. Of interest, mutations found in solid tumors can be drivers in hematologic malignancies. For instance, BRAF mutations are observed in approximately 60% of melanomas and predict response to the BRAF inhibitor vemurafenib. Recently, it has been shown that these mutations also characterize hairy cell leukemia, and this disease can respond to vemurafenib as well.\(^2\) In the era of molecular profiling and targeted therapy, traditional disease nosology may therefore need to be re-examined.

Understanding the underlying molecular biology of disease, and successfully acting on it, has advanced significantly faster in hematologic malignancies than in solid tumors. This may be, in part, a result of the fact that molecular evaluation is readily available through peripheral blood or bone marrow assessment at the time of diagnosis, relapse, and progression in hematologic malignancies (Fig. 3). In the case of solid tumors, there has been reluctance to perform repeat biopsies. However, there is mounting evidence that the molecular makeup of these malignancies evolves over time and space as it reveals new genetic targets, not present at diagnosis, which, untreated, may lead to mixed responses or progression. It is also likely that solid tumors are considerably more
genomically unstable than hematologic tumors. These data strongly suggest that repeat tissue biopsies may be needed with each relapse in solid tumors. In the future, newer technology that permits molecular profiling via analysis of blood samples from patients with solid tumors may be used.

THE SUCCESS STORY OF CHRONIC MYELOGENOUS LEUKEMIA: IS IT ABOUT TIME?

Chronic myelogenous leukemia (CML) exemplifies the evolution that occurs in most tumors but, in CML, this evolution is more clearly demarcated clinically, enabling its investigation. Inadequately treated, CML inevitably evolves from an early chronic-phase disease to a more aggressive accelerated phase, and then to the terminal blast transformation phase. Before the molecular era, patients inevitably succumbed in a median of 4 years. Treatments that controlled blood counts were, by and large, cosmetic, as they had minimal effect on disease evolution and survival. With the advent of molecular therapeutics, the outcome of CML has undergone a stunning transformation, with the median survival now being up to 20 to 25 years and counting. Since the median age of diagnosis is 60, patients can, for all intents and purposes, anticipate a normal life expectancy.

It is often claimed that CML is unique in some way, and that this uniqueness explains our ability to treat it so successfully as compared to solid tumors. In particular, many investigators claim that CML is a much simpler disease than solid tumors, being driven by a single actionable abnormality: BCR-ABL. In contrast, investigators commonly claim, each solid tumor is complex, and harbors multiple molecular drivers. Therefore, when solid tumors are treated with matched targeted agents, patients respond early on, but then develop resistance and experience relapse. Improvements in overall survival are sometimes seen, but they are often measured in weeks or months, not decades. However, if we examine these comparisons to CML more closely, it is apparent that there are basic flaws in the analogies. Indeed, if we look at the blast transformation stage of CML—a stage in many ways analogous to metastatic disease in solid tumors—we find that its treatment outcome is remarkably similar to that observed in solid tumors. Using imatinib or similar agents that specifically antagonize the aberrant BCR-ABL results in response rates of only approximately 15% in blast transformation; furthermore, all patients experience relapse, and median survival is about 1 year. These outcomes are remarkably similar to those seen using matched targeted therapy in metastatic solid tumors. However, if imatinib and similar second-generation BCR-ABL inhibitors are given to patients with newly diagnosed CML, the response rate leaps to near 100%, and median survival increases to over 20 years. Furthermore, allowing CML to evolve, by waiting beyond chronic phase to treat patients, is associated with a precipitous fall in response rates. Metastatic solid tumors and CML in blast crisis share their poor outcome and lessons learned from the CML story perhaps could be applied to targeted therapy in solid tumors.28

MOLECULAR PROFILING AND THE RECLASSIFICATION OF CANCER: FUTURE DIRECTIONS

The field of molecular profiling is an example of the transformative changes potentially conceivable in the field of clinical oncology. These changes may be driven by a convergence of factors, including a tidal wave of powerful new molecular technologies as well as the foreseeable availability of potent drugs with known targets in the clinic. Despite the promising outlook of molecular profiling as a discovery tool, its implementation in the clinic has been so far slow and incremental. Below we outline what we have learned so far and the limitations going forward.

There is now increasing evidence to support a rethinking of our understanding of tumors, as follows:

- Disease classified by light microscopy alone as derived from specific organ systems may not adequately segregate tumors for therapy.
- As a counterpoint, disease classified by molecular profiling alone may have therapeutic limitations as BRAF inhibition in colorectal cancer does not seem to be as effective as BRAF inhibition in melanoma.
- Malignancies may be classified both based on tumor of origin and their molecular aberrations, and this information has prognostic and predictive implications.
- Tumors classified histologically (for instance, lung, colon, or breast cancers) may be composed of hundreds of
molecular disease subsets with intratumor heterogeneity increasingly observed for genomic aberrations.

- When using therapies targeted against specific driver molecular aberrations, responses are dependent on selecting patients whose tumors harbor the appropriate target.
- Molecular profiling reveals that molecular aberrations do not necessarily segregate with organ of origin.
- Vastly different tumors with similar molecular profiles often have responses to the same targeted agent. However, this is not always true. It is unclear if certain tumors bearing a target fail to respond because they originate in a different organ or because they bear coexisting molecular aberrations that affect responsiveness.
- Since histologically similar diseases are comprised of hundreds of molecular subgroups, single tests such as those in companion diagnostics are not practical for identifying patient populations. In addition, the use of multiple companion diagnostics would require immense amounts of tissue and be exorbitantly expensive. Affordable multiassay technology that tests for hundreds of molecular aberrations at once are increasingly becoming a routine part of the diagnostic work-up of patients with cancer.
- There is tremendous heterogeneity emerging in the molecular profile of metastatic solid tumors both within the same patient and between tumors of the same histopathologic subtype. Therefore, even if these tumors respond initially, benefit is often short-lived. Individualized combinations of agents will be required to rationally treat these tumors.
- Metastatic tumors are complex and evolving and may require rebiopsy when progression occurs, as emerging molecular changes drive the appearance of resistance. Blood tests that are sensitive enough to detect genomic changes in circulating cells or circulating tumor DNA are under development and, in the future, may provide a more complete picture of a patient’s aberrant genomic landscape.
- Transformative changes in the outcome of CML occurred by using matched targeted therapy in newly diagnosed disease. This approach increased median survival from 4 years to over 20 years. Bringing drugs with proven activity from the metastatic setting to the front line has been exemplified by trastuzumab, a HER2-targeted therapy, which is now the standard of care in the adjuvant treatment of HER2-overexpressed breast cancer. It is not known if using matched targeted agents in many other newly diagnosed solid tumors would or would not have a similar transformative effect, as the vast majority of studies with matched targeted agents have been in metastatic disease.

There are still multiple challenges and limitations in our ability to successfully apply molecular profiling in the clinic, as follows:

- Profiling of tumors, especially with next-generation sequencing methodologies, may at times reveal hereditary aberrations. There is a need to address complex ethical issues related to these codiscoveries. Counselors should be available to patients who undergo profiling, and the patients should know in advance that hereditary abnormalities may be uncovered.
- The bioinformatics for processing whole genome datasets still requires refining. As a result, for now, real-time data is more easily attainable in the clinic with restricted gene sets, usually consisting of 50 to about 250 genes. It is anticipated that the bioinformatics capabilities to analyze more complex datasets will soon take a leap forward and resolve these challenges.
- Having a molecular profile but being unable to act on it because existing drugs are not being tested or covered for that histologic indication is a major barrier to progress that must be overcome. The clinical trial system as well as the system of financial coverage for approved drugs is inadequate for the current reality. These antiquated systems were created to test individual drugs across unselected patient populations. Even a more advanced approach that tests agents or regimens across selected patient populations is deficient, since we are finding that each patient may have a unique set of molecular drivers that requires a customized cocktail of drugs for best treatment. Therefore, there needs to be a new paradigm for clinical trials as well as for coverage decisions for approved drugs. We suggest that the “strategy” of using molecular markers to navigate to specific drugs or combinations must be ratified, and that its validation should supplant the need to test each drug or combination for each indication—since the latter may simply not be practical or possible.

Disclosures of Potential Conflicts of Interest

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References