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Precision Medicine Initiative Showing Early Signs of Success

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In his state of the union address, President Obama implored, "I want the country that eliminated polio and mapped the human genome to lead a new era of medicine—one that delivers the right treatment at the right time." The Precision Medicine Initiative that he was introducing aims to do just that for cancer patients, to discover an individualized patient- and tumor-specific blueprint that will indicate precisely the best therapy to eradicate the cancer without harming the patient. There are already early success stories, such as Gleevac, a drug which effectively targets a single genomic abnormality that is responsible for a common type of leukemia, and Tarceva, which targets a specific group of mutations in a subset of lung cancers, among others. Many additional drugs are in the Pharma "pipeline", targeting genes and pathways that are known to be significant in cancer initiation and growth. Patients are sometimes able to access these drugs, and drugs that have been approved for another purpose, through enrollment in a clinical trial, or by appealing for "off-label" use. With increasing frequency, finding a genomic abnormality in the tumor provides the indication for accessing these drugs and trials.

Forseeing patient need (and demand), many laboratories across the country have begun offering genomic profiling of tumors. Most of these are large academic centers, large reference laboratories, or completely new laboratories created just for this one purpose. A few larger private pathology groups, such as CellNetix Pathology, are also performing NGS testing. Some laboratories target only a few genes, some target tens or hundreds of genes, and some examine the whole exome or even genome. Some look at point mutations and small insertions and deletions, while some look at large segments of DNA that may be duplicated or lost, along with structural variants in the DNA. Some use premade "kits" and some have created custom panels. The segment of each gene examined can vary, and the "depth" of interrogation of each point in the segment examined can also vary. Similarly, the technical and clinical interpretation can be done using a variety of methods, and with a variety of intent. The aberrations discovered may just be listed, or they may be matched with information regarding significance in cancer, or in the specific tumor. Associated information regarding drugs and clinical trials may be provided. Also, while standards have recently been defined for NGS assay performance and validation (through Palmetto MolDx), there is no firm requirement for individual laboratories to meet these requirements. This leads to insecurity regarding the use and meaning of NGS results for cancer treatment, and uncertainty in the payer community regarding what exactly they are being asked to pay for.

An additional layer of uncertainty arises after NGS results are

produced. Integration of methods that have not necessarily been proven clinically, on this scale and with this regularity, is in many ways a new mode of practice for oncologists, who admirably aim to practice evidence-driven medicine and to remain within practice guidelines. Even when patients have exhausted all other options, or when standard treatment options have little chance of success, how to best integrate a novel targeted agent is still up for debate. Our oncologist colleagues at the Swedish Cancer Institute (SCI) in Seattle, in close collaboration with CellNetix Pathology, have taken a conservative approach in this area, attempting when possible to use these agents within the structure of a clinical trial, and when that is not possible, using one agent at a time, within the structure of the SCI Personalized Medicine Research Program registry. A biweekly multidisciplinary Molecular Tumor Board provides the opportunity to discuss these decisions with colleagues. This system assures that the outcomes of treatment are incorporated into the collective body of knowledge, while allowing patient access to agents that could improve wellness, disease free progression, and even survival. When approached within a deliberate, organized, ethical practice structure, this approach shows that genomic information can be used responsibly to help both current and future patients.

If we can accept that there are reasonable precautions that can be taken to ensure that testing meets high quality standards, and that the information produced is being applied appropriately, the biggest remaining concern for the implementation of a Precision Medicine Program is patient access to testing and treatment, which often is limited, due to a lack of reimbursement by government and private payers. Several concerns have led to slow adoption of this testing by payers, a few of which are outlined below.

In addition to the previously addressed concerns regarding quality, variability, and clinical application, many payers have concerns about the sheer volume of data produced by NGS testing. Many NGS cancer panels, including ours at CellNetix Pathology, are based on common cancer pathways and available targeted drugs, rather than specific genes that have been proven to be relevant for a specific tumor type. Since we have the capability to look at truly massive amounts of data, we are able to expand this focus to anticipate future directions in cancer therapy as well, sometimes resulting in large numbers of genes and segments examined. Many payers are uncomfortable with the "extra" data produced, and also with abnormalities that may be discovered that do not currently have a documented effect in the tumor type examined. However, if we exclude these "extra" targets, we run the risk of missing the unexpected tumors that may respond to a given drug, now or in the future, which is one of the biggest benefits of this testing strategy. A better approach is to assure that everyone involved understands the significance of the data, and has a strategy for application of the data clinically, to avoid "overinterpretation" of insignificant aberrations. This is ideally done in a practice setting that allows for close interaction between the oncology and pathology teams.

Payers also hesitate to provide access to tests that will open the door to some of the most expensive cancer drugs on the market, unless they already have documented benefit and value. The high price of cancer drugs has been a prominent topic, both in academic forums (Dr. Saltz at the recent ASCO 2015 meeting), among oncology professionals (118 oncologists commentary in Mayo Clinic Proceedings, this month), and in the popular media. While this problem is more complicated, and probably more difficult to solve, it does make sense to try to use this resource in the most responsible manner possible. Defining the best group of patients for access to these very expensive agents seems like a prudent strategy. If the test is not covered, and performed in an optimal setting, patients will likely still be able to access data of some sort, given the growing number of laboratories in the arena. As the saying goes "the toothpaste is out of the tube". By covering genomic testing performed in a responsible manner with high quality controls, payers can ensure the quality of data available to them to make the difficult decisions regarding drug reimbursement, and can also assure that any outcomes or value assessments are reliable.

Given these constraints, one of the bigger hurdles for payers to overcome is the need to establish a framework for evaluating Precision Medicine testing and treatment. In the testing arena, this has been made difficult by unclear standards and coding. Payers must understand the basic principles of NGS testing in order to even ask the right questions regarding quality and coverage. Objective standards such as those recently proposed by Palmetto/

MolDx could help to assure that the laboratory is producing a quality test, and a laboratory-specific coding system, such as the MolDx z-code unique identifier system, could also help payers to readily identify what exactly a test covers. Finally, creative arrangements between payers, oncology groups, and laboratories, for the evaluation of outcomes and value data should be undertaken, to help an exciting but somewhat confusing field take form, and to fulfill our mandate of providing the "right treatment at the right time" for our patients.

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