Precision Diagnosis for Precision Medicine

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The Precision Medicine Initiative and a "Moonshot to Cure Cancer" were announced by President Barack Obama in two consecutive State of the Union addresses in January 2015 and 2016. The conceptual foundations of precision medicine in oncology extend back nearly two decades and the first formal definition of the term was published in 2009. Precision medicine has three essential attributes, namely:

1. A mechanistic understanding of the etiology and pathogenesis of disease
2. The ability to detect (that is, to diagnose in the clinical laboratory) specific causal factors
3. The ability to specifically treat the root cause(s) effectively

Most discussions of precision medicine focus on examples of precision therapeutics drawn from the "first mover" field of oncology. Since the regulatory approval of imatinib (GLEEVEC®) to treat chronic myelogenous leukemia (CML) in 2001, approximately 50 targeted drugs have subsequently been developed and approved to treat nearly three dozen types of solid tumors and hematologic malignancies.

Because of this focus on precision therapeutics, the critical role of precision diagnostics in laboratory medicine is sometimes overlooked. Let's take the diagnosis and treatment of CML as an example. Prior to the development of imatinib, the routine diagnosis of CML was specific but not precise. There is a cytogenetic abnormality in the leukemic cells called the Philad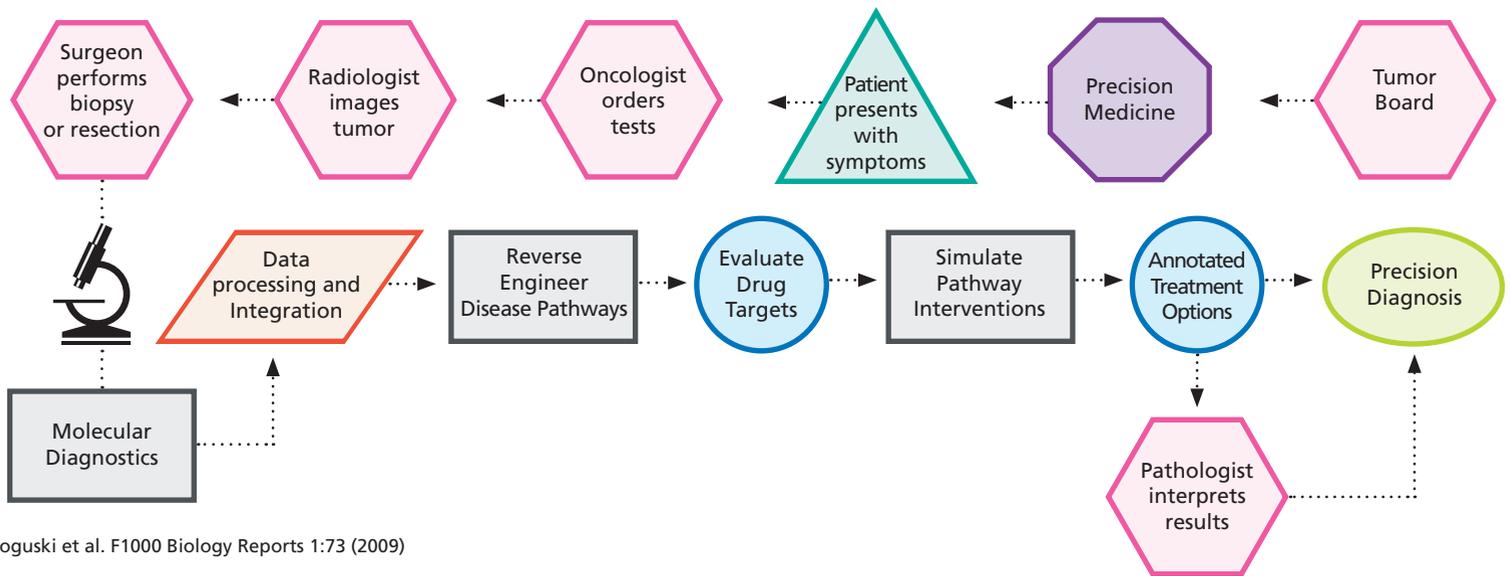elphia chromosome (Ph+) that represents a translocation between the long arms of chromosomes 9 and 22. Prior to imatinib, Ph+ CML was treated "imprecisely" with cytotoxic chemo- and radiation therapy. After it was established that the Ph+ translocation created a fusion oncogene, BCR-ABL, which represented the precise causal factor for CML, a precision drug was designed to target the unregulated kinase activity of the ABL enzyme. This combination of precision diagnosis with precision therapeutics thus transformed one type of cancer from a fatal disease into a manageable chronic illness.

Precision molecular diagnostics are commonly referred to as companion diagnostics and are mandatory prerequisites for the cost-effective use of targeted small molecule drugs or biologics. Classical examples include the use of vemurafanib (ZELBORAF®) in V600E mutant melanoma and trastuzumab (HERCEPTIN®) in HER2+ breast cancer. Without the precise laboratory diagnosis of the V600E mutation in melanoma or HER2 amplification in breast cancer, it would be useless, even harmful for patients and a waste of money for healthcare systems to prescribe and administer these costly drugs. Thus precision diagnostics not only lead to personalized medicine with better patient outcomes, but also to improved resource utilization and cost avoidance for healthcare systems.

These observations are consistent with the sometimes underappreciated power of pathology and laboratory medicine to greatly influence healthcare costs. Indeed, data and information from the clinical laboratory has been called

Workflow for Precision Diagnosis and Precision Medicine*

Surgeon performs biopsy or resection ← Radiologist images tumor ← Oncologist orders tests ← Patient presents with symptoms ← Precision Medicine ← Tumor Board

Molecular Diagnostics → Data processing and Integration → Reverse Engineer Disease Pathways → Evaluate Drug Targets → Simulate Pathway Interventions → Annotated Treatment Options → Precision Diagnosis

Annotated Treatment Options → Pathologist interprets results

*Boguski et al. F1000 Biology Reports 1:73 (2009)

a "new currency in the future of healthcare" because of its potential to support cost savings and cost avoidance system-wide. A 2009 report on the value of diagnostic innovation by The Lewin Group estimated that laboratory diagnostics account for less than 5% of hospital costs and about 1.6% of all Medicare costs but that laboratory test results influence as much as 60-70% of health care decision-making. Nevertheless, articulating the value proposition for precision diagnostics to payers has been challenging. This is due, in part, to an imbalance between rapid advances in the "technical components" of molecular tests and evidence of their clinical utility obtained through comparative effectiveness research. But it is also due to a serious lag in the education and training of physician-providers in the "professional components" of test utilization and interpretation due to exceedingly rapid advances in our precise, mechanistic understanding of the etiology and pathogenesis of diseases like cancer.

Again using oncology as an example, there are now approximately three dozen different types or subtypes of cancer in which assessment of about 60 molecular biomarkers can yield critical information that guides patient management and influences associated healthcare costs. This includes determination of the likelihood that an individual patient will or will not respond to a potentially costly precision therapeutic. A cutting edge example of this from late-stage clinical research involves the use of new "immune checkpoint inhibitors" (nivolumab (OPDIVO®) and pembrolizumab (KEYTRUDA®)) that block the interaction of the PD-1 T-cell receptor and its ligand PD-L1 on tumor cells. If a patient's tumor tissue does not express the PD-L1 ligand, will a therapeutic antibody that binds to PD-L1 (such as MPDL3280A) be of any benefit to the patient? A critical role for pathologists is, and will increasingly be, to determine scenarios that justify the utilization of what payers in the pre-precision era considered "esoteric" testing.

But it's not just about informing decisions whether or not to use expensive drugs or combination therapies in individual cases. Another important scenario is when molecular information about a patient's tumor can lead to treatment de-intensification and thus avoidance of both immediate treatment costs but also longer term adverse effects of intensive therapy on the patient. This scenario is currently being played out in both adult head and neck cancers and pediatric brain tumors. In the former case, cancers that have the molecular diagnosis of being human papilloma virus-positive (HPV+) have a much better prognosis than HPV-negative tumors.

Patients with HPV+ tumors can potentially be treated with protocols that greatly reduce the acute and long-term toxicities of chemo- and radiation therapies. Likewise, "risk stratification" through molecular subtyping of pediatric medulloblastomas is expected to reduce serious and long-term adverse effects of intensive therapy that can be avoided in lower-risk patients.

Precision diagnostics is a fulcrum in the changing landscape of precision medicine allowing for effective implementation of a value-based healthcare model. The value proposition of precision molecular testing for cost-effective patient care is becoming increasingly clear.

[1] http://f1000.com/prime/reports/b/1/73
[2] http://www.orchardsoft.com/files/white paper value lab.pdf
[3] http://thehill.com/sites/default/files/acla lewinvalueoflabsxdxreport o.pdf

Mark Boguski M.D., Ph.D. is Co-Founder and Chief Medical Officer of Precision Medicine Network™ and has served on the faculty of Harvard Medical School where he founded the Genomic Medicine Initiative in 2009. Dr. Boguski is a pioneer in the fields of bioinformatics and genomics and has previously held faculty positions at the Johns Hopkins University School of Medicine, the U.S. National Institutes of Health and the U.S. National Library of Medicine and as an executive in the biotechnology and pharmaceutical industries. He is a former Vice President of Novartis, a Visionary and Influencer according to the Personalized Medicine Coalition and was credited by Forbes as the originator of the term "precision medicine." Boguski is a member of the U.S. National Academy of Medicine, the American College of Medical Informatics and a Fellow of the College of American Pathologists.