H
istorically, the treatment of cancer has relied on the
application of cytotoxic chemotherapeutic regi-
mens chosen empirically based on the cancer’s site
of origin. This approach has seen iterative improve-
ments over 5 decades resulting in today’s modern
chemotherapy that can be delivered in the outpatient setting
with manageable side-effect profiles and quality clinical out-
comes. However, the advent of novel diagnostic technologies is
beginning to usher in an era of precision cancer medicine, de-

defined by the molecular characterization of a tumor to identify
actionable alterations, followed by treatment with therapeutics
that specifically target the alteration. Actionable alterations
are variably defined, but are broadly classified as scientifically
validated genomic alterations for which a targeted therapeutic
exists.

In the precision medicine approach to cancer, treatment is
selected on the basis of genomic or molecular abnormalities
specific to the cancer, rather than anatomical or histological
disease origins. While outcomes data regarding precision can-
cer medicine are still maturing, the promise of the approach
includes improved outcomes, measured by survival and quality
of life metrics, and economic gains, as ineffective regimens and
severe side effect events are minimized. Critical evaluation of the
precision medicine promise remains in its earliest stages as the
appropriate clinical implementation of precision tech-
nologies continues to evolve.

Clinically implementing precision cancer medicine
and actively treating patients with targeted therapies
continues to be a challenge for health care providers.
Questions regarding the interpretation of genomic re-
sults, costs associated with testing, timing of targeted
treatment implementation, and the accessibility of
therapies suggested by genomic tests remain signifi-
cant hurdles for providers and patients, alike. While the
answers to these questions are readily available, apply-
ing the solutions to enable precision cancer medicine
for an entire patient population, and implementing the
approach in programmatic fashion remains elusive.

Seek a Better Standard of Care
In the precision medicine approach to cancer, treatment is selected on the
basis of genomic or molecular abnormalities specific to the cancer, rather than
anatomical or histological disease origins.

Clinical Implementation of Precision
Cancer Medicine
To help determine the best methods to clinically im-
plement precision cancer medicine as a program, we
initially established a personalized medicine clinic as
a pilot. Patients with advanced, refractory cancer were
referred to the personalized medicine clinic where
they received education and information about can-
cer genomics testing to determine if it might be ap-
propriate for them. A follow-up visit to the personal-
ized medicine clinic was then conducted 2-3 weeks
later to review genomic testing results with the patient
and to discuss treatment implications. Patients then
were referred back to their primary treating oncolo-
gist, with an in-depth interpretation of the genomic
results and a list of treatment options to consider.

The Clinical Implementation of
Precision Cancer Medicine

By Derrick Haslem, MD, and Lincoln D. Naudauld, MD, PhD
Armed with this information, implementation of any targeted treatment options remained solely at the discretion of the primary oncologist. A key feature of our precision genomics program has been the input of the molecular tumor board (MTB). Modeled after traditional tumor boards, the MTB comprises experts in cancer genomics and meets regularly to review and evaluate genomic testing results. The end goal of the MTB is to provide a consensus interpretation of the alterations found in a patient’s tumor and how the alterations might impact the treatment plan for that patient. For example, a patient with refractory metastatic lung cancer whose tumor harbors KRAS, FGFR1, and CDK6 alterations might be a candidate for several clinical trials, each investigating selective inhibitors of those pathways; or, the treating oncologist may wish to employ an approved drug off label. This scenario illustrates a common challenge in precision medicine—when a tumor harbors multiple actionable mutations, which of the genes or pathways should be targeted? In such cases, our molecular tumor board generally follows a prioritized algorithm where the first priority is to provide patients with on-label treatments or clinical trial enrollment, whenever possible, followed by off-label targeted treatments, and follow-up testing on new biopsy specimens. The collective experience and insight of a MTB often is the key to determining the best path forward in such cases. The MTB also can provide significant confidence for providers who may have less experience interpreting molecular testing results.

The commitment from providers to broadly adopt precision medicine, and the ability of payers to justify reimbursement for this approach, largely hinge on the clinical outcomes associated with this treatment paradigm. The end goal of the MTB is to provide a consensus interpretation of the alterations found in a patient’s tumor and how the alterations might impact the treatment plan for that patient. Armed with this information, implementation of any targeted treatment options remained solely at the discretion of the primary oncologist.

A key feature of our precision genomics program has been the input of the molecular tumor board (MTB). Modeled after traditional tumor boards, the MTB comprises experts in cancer genomics and meets regularly to review and evaluate genomic testing results. The end goal of the MTB is to provide a consensus interpretation of the alterations found in a patient’s tumor and how the alterations might impact the treatment plan for that patient. For example, a patient with refractory metastatic lung cancer whose tumor harbors KRAS, FGFR1, and CDK6 alterations might be a candidate for several clinical trials, each investigating selective inhibitors of those pathways; or, the treating oncologist may wish to employ an approved drug off label. This scenario illustrates a common challenge in precision medicine—when a tumor harbors multiple actionable mutations, which of the genes or pathways should be targeted? In such cases, our molecular tumor board generally follows a prioritized algorithm where the first priority is to provide patients with on-label treatments or clinical trial enrollment, whenever possible, followed by off-label targeted treatments, and follow-up testing on new biopsy specimens. The collective experience and insight of a MTB often is the key to determining the best path forward in such cases. The MTB also can provide significant confidence for providers who may have less experience interpreting molecular testing results.

The commitment from providers to broadly adopt precision medicine, and the ability of payers to justify reimbursement for this approach, largely hinge on the clinical outcomes associated with this treatment paradigm. The question of whether precision cancer medicine positively affects clinical outcomes has remained largely unanswered. However, the commitment from providers to broadly adopt precision medicine, and the ability of payers to justify reimbursement for this approach, largely hinge on the clinical outcomes associated with this treatment paradigm. Thus, the primary metrics involved in a clinical outcomes analysis should include survival measurements (progression-free survival and/or overall survival), and an overall cost analysis. Valuable secondary outcomes include quality of life, adverse events, and morbidity.

The Germline State in Cancer Genomics

An important concept in genomic testing is the reality that tumor genomics reflect the germline state. In other words, when an alteration is detected in a tumor, it can be a somatic alteration or an inherited germline mutation. For example, somatic tumor testing in a twenty-year old patient with sarcoma may identify a variant in TP53, which raises the possibility of Li Fraumeni Syndrome; or, somatic tumor testing in a fifty-year-old patient with breast cancer may identify a BRCA1 mutation raising the possibility of inherited breast cancer. Each scenario raises a separate question with complicated implications, but both scenarios illustrate the reality that somatic testing reflects the germline state, which is perhaps one of the most common concerns surrounding cancer genomics amongst community and academic oncologists, alike.

The concern providers and institutions have about germline mutations “hiding” in somatic testing is centered on the concepts of responsibility and liability. The applicable question in these cases is whether a physician, or healthcare institution, is required to reflexively pursue germline testing of any somatic variant that may represent a germline variant in order to rule out an inherited familial cancer syndrome. This dilemma is occasionally cited by payers as rationale against large-gene panel testing in cancer treatment. In the absence of sufficient clinical outcomes data in favor of comprehensive somatic testing, there may be some reluctance to pay for somatic testing that theoretically leads to additional germline testing; the value of which to the patient remains unclear, while the costs are high.
Determining which patients warrant further germline testing (and which patients can safely forego additional testing) can be difficult. While there are many viable approaches to address this situation, the Intermountain Precision Genomics program has employed the advice of the MTB and genetic counselors in these cases. Fortunately, decades-old tools, such as family history and a careful patient history, often can help in the appropriate triage of patients. When the MTB determines that a particular alteration may reasonably represent a germline variant, those patients are referred to genetic counselors for follow-up. In some cases, such as BRCA mutations found in breast cancer patients, we reflexively perform germline testing as standard protocol.

**Pitfalls and Cautions**

Implementation of a clinical cancer genomics program can be complicated, particularly given the various steps involved. Even after molecular diagnostic testing, bioinformatics, interpretation, and drug procurement, there are still a number of pitfalls that can complicate the endeavor. These include tumor heterogeneity, tumor evolution, and epigenetic modifications, amongst others.2

**Tumor Heterogeneity** refers to the presence of multiple clonal cell populations within the same tumor (intra-tumoral heterogeneity), or different clonal populations between different metastatic sites derived from the same primary tumor (inter-tumoral heterogeneity). This principle was exquisitely demonstrated by Gerlinger et al., who sequenced biopsy specimens from multiple sites within the same renal cell carcinoma primary site, as well as multiple biopsy specimens from different metastatic sites of the same patient.3 The genomic findings were diverse and differed between intra-tumoral biopsies and inter-tumoral biopsy sites. These findings confirmed what scientists and physicians have long believed; genomic diversity within human cancers is significant. This principle is particularly relevant in the application of precision medicine. Typically, only a single biopsy sample is sequenced to identify actionable mutations. However, the molecular alterations identified in a given sample may only represent a minority population of clonal tumor cells. Identification and targeting of an actionable mutation might, therefore, only target a small percentage of the tumor. Measuring a clinical response in that case may be complicated by a lack of response in the remaining majority of cancer cells. Conversely, a biopsy that is fortuitously obtained from the majority clonal population may reveal an actionable mutation that, when targeted with treatment, could yield a significant and durable clinical response. In both cases, precision cancer medicine may have been utilized, but only one of the patients might reasonably enjoy a treatment response.

**Tumor Evolution** is a related, and equally confounding phenomenon in precision cancer medicine. Given that diverse subclonal populations populate tumors, targeting a single actionable mutation can lead to selection of subpopulations that are negative for the targeted alteration. This scenario may result in brief or durable responses, but the end result of tumor progression ultimately will be realized as the resistant clones gain a selective advantage. This principle has been validated repeatedly in various malignancies, including leukemias, gliomas, and various other solid tumors.4-7

While the reality of tumor evolution may appear to render genomic-targeted therapies futile, the presence of inter- and intra-tumor evolution presents novel treatment opportunities. For example, a bladder cancer patient in whom an actionable FGFR alteration is identified, may respond to an FGFR inhibitor for an extended period, only to progress with ongoing treatment. In such an instance, tumor evolution yielding resistant mutations is a likely culprit. Biopsy and re-sequencing in this instance may identify novel actionable alterations that have been selected, or acquired, during the course of tumor evolution. These acquired alterations represent novel treatment opportunities, and the entire cycle is repeated. While this approach is far from validated, theoretically it is feasible, and case studies reporting on this phenomenon continue to mount.

**Epigenetic modifications**, including DNA methylation and histone acetylation, are well-described phenomena that occur normally in a variety of cellular states. These events strongly influence and directly regulate transcription and gene expression. While the diagnostic measurement of epigenetic modifications is not yet routinely utilized in clinical cancer care, the impact of
these modifications appears to play a significant role in precision medicine. As an example, activating mutations in the BRAF gene frequently occur in malignant melanoma and are predictive of response to BRAF and MEK inhibitors.\textsuperscript{8-10} However, the same BRAF alteration found in other cancer types, such as colorectal cancer, does not appear to confer the same exquisite sensitivity to direct and downstream molecular inhibition. This raises the question: Why does a BRAF mutant melanoma respond well to RAF signaling inhibition while BRAF mutant colorectal cancer does not? The answer may lie in the epigenetic state of those different cancers that were derived from different tissues of origin. The phenomenon of differential response by different tumor types to the same molecular inhibitor is clearly more complicated than simply identifying an activating DNA mutation. Multiple factors, including the epigenetic state, tumor microenvironment, and immunological activation are all important determinants of tumor responsiveness that will undoubtedly play an ongoing role in precision cancer medicine.

**Summary**

Precision cancer medicine is a rapidly evolving science. The confluence of cost-effective genomic technologies and the increasing number of targeted therapies has placed clinical cancer care in a unique and envious position. Providers now have the means to comprehensively interrogate a patient’s sample, evaluate the identified variants, and select a targeted therapy to treat their patient’s cancer. These realities are ushering in an exciting new model in cancer care.

Obstacles to the implementation of precision medicine remain for both the patient and provider—interpretation of genomic testing is difficult, procuring targeted therapies for patients with refractory disease can be arduous, and the clinical outcomes supporting the broad application of genomic medicine are just beginning to mature. In addition, the complexities of cancer cell biology, including tumor heterogeneity and evolution, and the vast cell signaling networks affected by various targeted treatments, combine to slow our understanding of the impact precision medicine has on the disease itself.

In spite of the hurdles that exist, and in light of the breathtaking responses that can occur, a tidal wave of investment in precision medicine continues. Institutions, academic and non-academic alike, have announced precision medicine centers in diverse locations across the country. Likewise, pharmaceutical companies and other industry stakeholders are developing the necessary therapies and diagnostic capabilities to support the widespread adoption of precision medicine.

The coming months and years will yield significant clinical trial data regarding the impact on outcomes metrics, such as survival and health care costs, associated with genomic-guided precision medicine, while further scientific advancements will open additional treatment options. As positive outcomes data accumulate and experience with clinical implementation matures, the precision medicine paradigm may become the standard of care for patients with advanced cancer.

**References**