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Cancer Diagnostics and Molecular Pathology

Key Lessons Learned from Moffitt's Molecular Tumor Board: The Clinical Genomics Action Committee Experience

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Abstract

Background. The increasing practicality of genomic sequencing technology has led to its incorporation into routine clinical practice. Successful identification and targeting of driver genomic alterations that provide proliferative and survival advantages to tumor cells have led to approval and ongoing development of several targeted cancer therapies. Within many major cancer centers, molecular tumor boards are constituted to shepherd precision medicine into clinical practice.

Materials and Methods. In July 2014, the Clinical Genomics Action Committee (CGAC) was established as the molecular tumor board companion to the Personalized Medicine Clinical Service (PMCS) at Moffitt Cancer Center in Tampa, Florida. The processes and outcomes of the program were assessed in order to help others move into the practice of precision medicine.

Results. Through the establishment and initial 1,400 patients of the PMCS and its associated molecular tumor board at a major cancer center, five practical lessons of broad applicability have been learned: transdisciplinary engagement, the use of the molecular report as an aid to clinical management, clinical actionability, getting therapeutic options to patients, and financial considerations. Value to patients includes access to cutting-edge practice merged with individualized preferences in treatment and care.

Conclusions. Genomic-driven cancer medicine is increasingly becoming a part of routine clinical practice. For successful implementation of precision cancer medicine, strategically organized molecular tumor boards are critical to provide objective evidence-based translation of observed molecular alterations into patient-centered clinical action. Molecular tumor board implementation models along with clinical and economic outcomes will define future treatment standards. ***The Oncologist*** 2017;22:144–151

Implications for Practice: It is clear that the increasing practicality of genetic tumor sequencing technology has led to its incorporation as part of routine clinical practice. Subsequently, many cancer centers are seeking to develop a personalized medicine services and/or molecular tumor board to shepherd precision medicine into clinical practice. This article discusses the key lessons learned through the establishment and development of a molecular tumor board and personalized medicine clinical service. This article highlights practical issues and can serve as an important guide to other centers as they conceive and develop their own personalized medicine services and molecular tumor boards.

Introduction

Advances in genomic technology have opened new options for cancer treatment [1–4]. Successful identification and targeting of the driver genomic alterations that provide proliferative and survival advantages to tumor cells have led to approval of several targeted cancer therapies, such as imatinib for *BCR-ABL*-positive chronic myelogenous leukemia [5], vemurafenib and dabrafenib for *BRAF V600*-mutated melanoma [6, 7], and crizotinib and ceritinib for *ALK*-rearranged non-small cell lung cancer (NSCLC) [8, 9]. As genomic sequencing and targeted therapies have demonstrated clinical efficacy, the current pharmaceutical pipeline contains several agents targeting altered cancer genes across many cancer types. The increasing practicality of genomic sequencing technology has spurred investigators to further understand the

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clinical impact of these mutations, and analysis of the cancer genome is increasingly becoming routine clinical practice [10–13].

The disease courses of many patients progress beyond U.S. Food and Drug Administration (FDA)-approved therapies or National Comprehensive Cancer Network guidelines on the basis of alterations detected in their tumor [14]. This has led to identification of clinical trials, "off-label" treatment, or compassionate-use protocols in attempts to objectively provide options to prolong survival and increase quality of life. Within many major cancer centers, molecular tumor boards are constituted to shepherd precision medicine into clinical practice [15–17].

Materials and Methods

In July 2014, the Clinical Genomics Action Committee (CGAC) was established as the molecular tumor board companion to the Personalized Medicine Clinical Service (PMCS) at Moffitt Cancer Center in Tampa, Florida. CGAC was conceived to aid in the rational implementation of cancer genomics (and other ways of individualizing treatment) by providing a multidisciplinary assessment of advanced diagnostic strategies and complex clinical results. The committee provides oversight and guidance to the PMCS and discusses patients with all types of cancer to develop consensus on therapeutic recommendations, enabling the translation of scientific findings into evidence-based recommendations for individualized treatments. Specific responsibilities of CGAC include the following: (a) providing a consensus forum for determining objective patient management recommendations when multiple therapy options are being considered or when a variant of unclear therapeutic significance is identified, (b) performing multidisciplinary assessment of requests for introduction of precision medicine assays at Moffitt Cancer Center, and (c) assisting in the development of Moffitt electronic health record clinical decision support rules that alert clinicians to actionable variants.

Process

The PMCS reflexively receives results of all next-generation tumor sequencing (NGS) panels ordered as part of clinical care at Moffitt. These include in-house developed NGS panels in addition to those sent to reference laboratories. NGS results are reviewed at a weekly PMCS meeting, with PMCS interpretation and recommendation provided to the ordering clinician through email and a clinical consult note in the electronic health record (EHR) for all cases (Table 1). Controversial or challenging cases are discussed at the monthly CGAC meeting ($n = 59$; mean, 2.3 cases per meeting) (Table 2) to establish a group consensus related to the significance of alterations detected, possible therapeutic options, and the recommended procession of therapy. Once consensus has been achieved, consultation reports, including the key points of the CGAC discussion, are generated, entered into the EHR, and communicated to the ordering clinician and subsequently the patient. Clinical trial enrollment is facilitated, or if off-label therapy or compassionate use is pursued, the PMCS offers assistance in obtaining the medication and insurance approval (Fig. 1).

Several practical lessons of broad applicability have been learned through the establishment and initial 1,400 patients of

Table 1. Demographics of all Personalized Medicine Clinical Service cases as of June 27, 2016 ($n = 1,402$)

Category/subgroup	Cases (*n*)	Proportion of total with data (%)
Sex		
Male	757	53.99
Female	644	45.93
Transgender	1	0.07
Race		
White	848	89.55
Black	53	5.60
Other	28	2.96
Asian	7	0.74
East Asian Indian	7	0.74
American Indian	4	0.42
Unknown/not reported	455	NA
Ethnicity		
Non-Hispanic	616	92.35
Hispanic	37	5.55
Other	14	2.10
Unknown/not reported	735	NA
Previous lines of treatment		
0	153	15.03
1	346	33.99
2	198	19.45
3	130	12.77
4	71	6.97
≥5	120	11.79
Unknown/not reported	384	NA
Cancer type		
Lung	240	17.25
Brain	183	13.16
CLL	160	11.50
Colorectal	103	7.40
Sarcoma	96	6.90
Melanoma	95	6.83
Breast	94	6.76
ALL	44	3.16
Lymphoma	42	3.02
AML	36	2.59
Unknown primary	32	2.30
Merkel cell	30	2.16
MDS	22	1.58
Salivary gland	19	1.37
Pancreatic	17	1.22
Thyroid	16	1.15
Head and neck, other	14	1.01
Kidney	13	0.93
Leukemia, other	13	0.93
Skin cancer (nonmelanoma)	12	0.86
Cholangiocarcinoma	10	0.72
36 others (<10 cases)	100	7.19

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; NA, not available.

Table 2. Cases presented at Clinical Genomics Action Committee meetings ($n = 58$)

Cancer type	Cases (*n*)
Sarcoma	11
Lung	10
Breast	8
ALL	4
Brain	4
Melanoma	3
Merkel cell	2
AML	2
Cholangiocarcinoma	2
Thyroid	1
Ovarian/AML	1
Mantle cell	1
Head and neck	1
Adrenocortical	1
DLBCL	1
Basal cell	1
Thymic	1
Chordoma	1
Thyroid/GIST	1
Colorectal	1
Cutaneous T-cell lymphoma	1

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MDS, myelodysplastic syndrome; GIST, gastrointestinal stromal tumor.

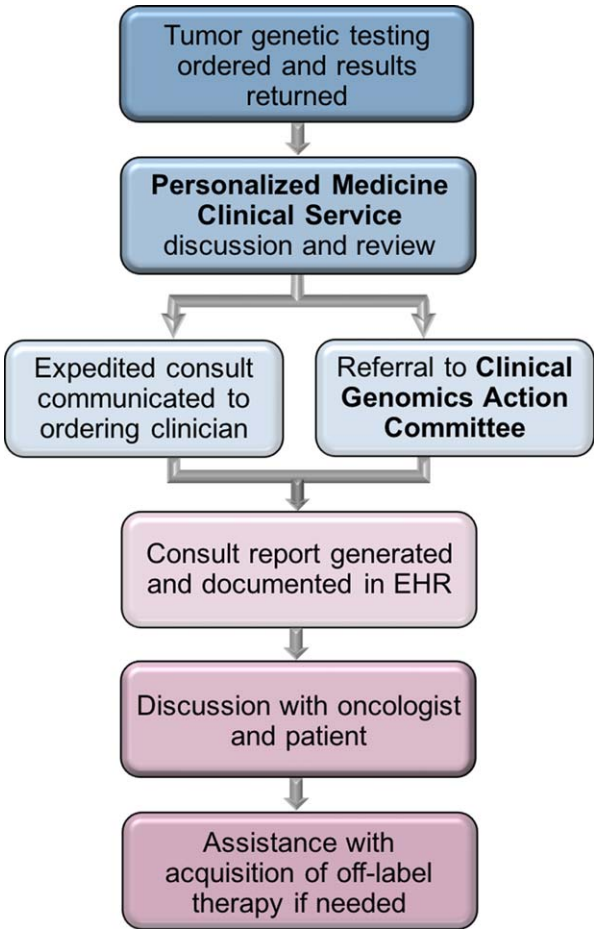

Figure 1. Tumor genome analysis workflow.
Abbreviation: EHR, electronic health record.

the PMCS and its associated molecular tumor board at a major cancer center.

Key Lessons Learned

Transdisciplinary Engagement

To accommodate the diverse results generated by broad tumor sequencing, a comprehensive, collaborative approach is needed. CGAC includes members from pathology, medical genetics, bioinformatics, translational research, laboratory science, pharmacy, patient representatives, nursing, social work, and physicians from across oncologic and hematologic diseases. Engagement from all of these groups is crucial to having a true transdisciplinary evaluation of the patient and their genomic information, and all are encouraged to stimulate discussion on potentially relevant findings even if those findings are outside of their designated specialty. Cases are typically presented by a member of the PMCS or a rotating fellow/resident, with clinical details supported by the treating physician. All experts in the room bring a unique perspective, and committee meetings present a unique opportunity to have representation from all of these groups in one place at a given time united to further the personalization of cancer care. While a particular patient case being discussed may revolve around a specific tumor type, lessons and insight from other clinicians in the room have proven helpful in describing their experience with the molecular aberrations and corresponding targeted therapy or evidence and developments in their field. The presence of both researchers and clinicians has enabled a bidirectional flow of information. Not only does cutting-edge research inform discussion of therapeutic options, but clinician practice of medicine and realities of the multipayer health care system help determine which information is of greatest utility.

As the molecular treatment of cancer increasingly becomes a part of standard care, the expectation is that molecular tumor boards will become essential much in the same way that disease-specific tumor boards are today. Community clinicians who may lack the resources to meet the forthcoming challenges can partner with large academic medical centers or use centralized molecular tumor boards. A side benefit of the multidisciplinary discussions is a greater appreciation for the perspectives of complementary disciplines. Molecular tumor boards should bring together a varied group of experts and function in a way that builds on existing structures and processes within the health system while maintaining the flexibility to adapt to new challenges and support the community in which they serve.

Following are some tips for the community practice. Most cancer patients in the United States are treated at community-

based practices [18] and thus are unlikely to have access to the molecular tumor boards concentrated at large academic medical centers. Self-contained, single-site molecular tumor boards in the community are typically not feasible because molecular tumor boards rely on a breadth of experts who are not always integrated into community practices (bioinformaticians and translational researchers, for example). Community oncologists seeking to provide highest-level care to their patients are faced with the challenge of developing and maintaining high-level expertise in interpreting and acting upon molecular reports, combined with mechanisms for clinical trial enrollment or finding alternate solutions.

Large registry trials, such as the American Society of Clinical Oncology's Targeted Agent and Profiling Utilization Registry (TAPUR), which offer a molecular tumor board component, may represent a current pathway for obtaining external advice on patients who have received NGS [19]. Other community practices may pursue an outsourced molecular tumor board from an academic partner institution, which would gain reciprocal value though increased genomic data and potential clinical trial participants. Alternatively, private molecular tumor boards composed of national experts may be developed to provide such services to community practices. Although community practices may not have the resources to support full-time in-house molecular tumor boards, alternatives, including partnerships with academic centers and regional and private tumor boards, allow for broader patient access to multidisciplinary expertise.

The Molecular Report as an Aid to Clinical Management

To promote implementation of tumor genomic data, alterations identified by NGS are communicated to clinicians by the test providers as a summarized molecular report. This molecular report serves as an aid to clinical management and represents the start of the process of molecularly targeted precision cancer therapy. However, there is a gap between the content of the lab reports and the clinical action that should result from the data. There are practical reasons for this gap (liability, customer autonomy, insufficient clinical context), but it is a major issue in getting the most out of the test.

The availability of dedicated personalized medicine experts, such as a personalized medicine consult service or a molecular tumor board, can help oncologists navigate the nuances of the report. To support a practitioner who orders the test or to aid patients who bring a large test report to their clinician, there needs to be a mechanism for external molecular reports to be assessed by the personalized medicine service or molecular tumor board. It is common for radiologists to reveal the relevance of a T1- versus T2-weighted magnetic resonance imaging examination or for pathologists to understand the role of specific stains when reviewing a biopsy specimen. This same principle can apply to the evaluation of the cancer genome.

Variability across reports from reference laboratories is also often not recognized by oncologists applying new tests. Understanding and interpreting results across the breadth of genes evaluated (from a single gene to the whole genome), the types of alterations detected (e.g., mutations, copy number alterations, rearrangements, translocations, fusions), and other factors (e.g., read depth, sequence coverage, the effect of the subclonal detection of mutant variants or equivocal levels of copy number variation) are critical. Evaluation of a genomic report, as with other specialty reports, requires an understanding of the capabilities and elements of the report.

Most reports include information curated from medical literature describing the function of the gene, the frequency with which it has been reported in the patient's cancer type and other cancers, any known prognostic role, and possible therapeutic strategies. This information is dynamic, and thus it is important to consider how it is being curated, from what sources, and how often. Within the report, clinical recommendations of therapies, including those for off-label use or clinical trials to be considered, can be broad and abundant. These recommendations are written to apply to a generalized patient population and logistically cannot account for patient-specific factors that are not shared with the sequencing lab. This becomes evident when the report supplies a recommendation for a clinical trial that the patient is ineligible for because of having received too many previous lines of therapy or multiple comorbidities, for example, or is not recruiting locally. The ordering physician and the supportive personalized medicine team should consider the relevance of the treatment options in a way that is personalized to individual patients, their clinical history, and their treatment preferences. The molecular tumor board therefore offers not only an opportunity to harmonize (or at least provide greater context) to the different test platforms but enables appropriate dialogue and personalization of results in order to use them in the context of patient history and preferences.

Clinical Actionability

The goal of the PMCS/CGAC is to assist the treating oncologist in the translation of molecular variants into clinical action for the individual patient. The clinical actionability of these variants includes providing the rationale for potential therapeutic options, contributing to diagnostic evidence, or helping prognosticate disease course. For a growing list of genomic variants there is clear impact on specific cancer therapies, often with corresponding presence in the FDA drug label (e.g., *KRAS*, *EGFR*, *ALK* fusions, and *ROS-1*). These variants are handled in the pathology report, with little added value from a PMCS or CGAC. However, most variants (>80% in our experience) do not have well-defined clinical consequence. The availability of a tumor genomics assessment supported by bioinformatics is a key tool for addressing the need for time, expertise, and resources.

Many commercial sequencing strategies focus on tumor tissue and therefore identify both somatic and germline variants. It has been reported that the absence of a matched germline control results in false-positive somatic mutation determinations [20]. There is a need to understand whether the variant is likely to be germline (and potentially associated with inherited cancer syndromes), somatic (and whether it has been observed before and in what types of cancer), and in a location in the gene that includes a biologically relevant domain on the resulting protein. Use of databases, such as 1000 Genomes Project or Exome Variant Server, will provide support of germline inheritance; ClinVar or the International Agency for Research on

Table 3. Informatics resources

Category/resource	Utility
Variants of unknown significance	
1000 Genomes Project (http://www.1000genomes.org/)	Provide a probability of the variant being germline
Exome Variant Server (http://evs.gs.washington.edu/EVS/)	Provide a probability of the variant being germline
Inherited Cancer Risk	
International Agency for Research on Cancer (IARC) (http://p53.iarc.fr/)	Frequency of a TP53 mutation in germline and tumor samples
HCI Breast Cancer Gene Prior Probabilities (*BRCA*) (http://priors.hci.utah.edu/PRIORS)	Data on all possible single nucleotide substitutions in *BRCA1/2*
ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/)	Association of a variant with an inherited disease
American College for Medical Genetics and Genomics (https://www.acmg.net/)	Association of a variant with an inherited disease
Variants from across cancer types	
cBioPortal (http://www.cbioportal.org/)	Frequency of a variant across cancer types and location of the variant in the functional domains of the gene
Catalogue of Somatic Mutations in Cancer (COSMIC) (http://cancer.sanger.ac.uk/cosmic)	Frequency of a variant across cancer types
Therapeutic association	
MyCancerGenome (http://www.mycancergenome.org/)	Association of mutation with tumorigenesis, related therapeutic implications, and available clinical trials
PharmGKB (https://www.pharmgkb.org/)	Interactive tool for researchers investigating how genetic variation affects drug response
Personalized Cancer Therapy Knowledge Base for Precision Oncology (https://pct.mdanderson.org)	Knowledge base resource for the implementation of personalized cancer therapy and integrating information about tumor DNA, RNA, and protein and metabolomics profiles with predicted therapy response
ClinicalTrials.gov (http://clinicaltrials.gov)	Searchable database that provides information about current ongoing clinical research studies

Cancer will indicate whether the variant has been associated with inherited disease.

Another assessment is the frequency of a somatic variant in such databases as cBioPortal or Catalogue of Somatic Mutations in Cancer (COSMIC) (Table 3). Understanding how often and where (i.e., which type of cancer) a variant has been observed will provide a level of confidence in calling it a somatic mutation and can broaden the search for impact (e.g., a variant that is rare in sarcoma but observed in 20% of NSCLCs gives guidance on where to look for gene-effect relationships). Many of the resulting variants are germline in nature, and most are not of direct relevance to therapeutic care, although focusing on smaller panels of cancer-related genes reduces this. To ensure that incidental germline findings receive appropriate follow-up, the PMCS has worked with Moffitt's Genetic Risk Assessment Service to develop a list of genes based on the American College of Medical Genetics and Genomics genes associated with inherited cancer syndromes [21] and other potentially actionable genes found on the somatic genomic panels but are supported by clinical literature as associated with inherited cancer syndromes that warrant patient referral if a mutation is reported. Clinicians and centers must be prepared for incidental findings, be able to recognize them, and know when and how to refer to genetic counselors and medical geneticists [22].

A common challenge in precision medicine is genomic variants, which are located in a functional protein domain and have possible functional consequences (e.g., nonsynonymous mutation, stop codon, frame shift) but have not been biologically characterized to the point of definitive recommendations. In the context of a patient case, variants of almost known significance (VAKS) are triaged differently than variants of known significance or variants of unknown significance and are a frequent subject of discussion at CGAC meetings because they may make the patient eligible for certain targeted therapies. Input from basic scientists helps to clarify the potential effect of the mutation and subsequently the affected pathways, triggering discussion of mechanisms of drug response. In the absence of other options, these data are tempting treatment targets, but this temptation has to be carefully weighed against therapeutic options available to the patient in question and the patient's prognosis. Molecular tumor boards should be prepared to face these molecular dilemmas and consider processes for handling them, ranging from withholding action until guideline consensus is established to developing a research enterprise to evaluate the variants. The presence of these variants as potential therapeutic targets can also feed back to researchers who may have the resources and interest to test VAKS for functional activity.

Getting Therapeutic Options to Our Patients

The PMCS is involved in the interpretation of a variety of different somatic genomic assays from different laboratories, each with its own unique clinical reports. An added value

Table 4. Personalized medicine consult note description

Consult note section	Description of section contents
Recommendation summary	The recommendations discussed in the actionable discussion are summarized and placed at the top of the consult to provide an easy reference for providers
Patient demographics and history of present illness	Provides the pertinent information needed regarding diagnosis details, pathology, scan results, and treatment history to assist with translating the genetic results into a specific recommendation that is patient specific. This includes the patient's desire for clinical trials or off-label drug options and information that helps to prioritize treatment options, including insurance status, ability to travel, and goals of treatment.
Genetic test information	The details of the genetic test are listed, including the date of sample collection, the site of collection, and the date of the genetic report
Significant genetic findings	All of the potentially actionable genes and associated mutations are listed along with copy number or allele frequency. Each mutation is discussed in terms of cancer biology and role in cancer growth, whether the alteration is known to be activating or inactivating, how common the alteration is in the patient's specific cancer, and preliminary information about potential drug therapy that may inhibit the target.
Variants of unknown significance	Genetic alterations that are reported but for which the effect of the alteration is not known are listed. Additionally, mutations that are benign germline alterations are also listed here.
Actionable discussion	The supporting data for each clinically actionable mutation discussed in the "Significant Genetic Findings" section is explained in more detail with cited literature to support treatment recommendations. Clinical trial literature is preferred; however, case reports and animal and in vitro data are also included to support treatment recommendations. Reasonable clinical trial options are also included based on patient factors.
Genetic risk assessment service referral?	Any reported germline mutations associated with hereditary cancer or other syndromes are briefly discussed with a recommendation to the genetic risk assessment service where appropriate. Recommendations and wording for this section are developed in collaboration with the clinical genetics team.
Final recommendations with level of evidence	A final summary of the treatment recommendation and level of supporting evidence is listed at the end

provided by the PMCS is operating beyond the more generic information provided and reporting it in a consistent, individualized format based on each patient's prior therapies and unique clinical characteristics (Table 4). This helps contextualize results, improving the clinical utility of each consult and enhancing implementation. An additional patient-centered goal of the clinical consult is anticipation of a patient's needs to consider future treatments beyond the next line of therapy. This is also an important consideration when weighing possible clinical trials. Reviewing the inclusion criteria for a particular trial may optimize the number of alternatives a patient may have. For example, if options A and B are both equally acceptable to the patient and supported by the medical team, but giving off-label option A before clinical trial option B would exclude the patient from option B, then a more favorable order for therapy should be considered.

Additional value of the clinical consult note may include facilitating off-label therapy by using the consult report as a summary of evidence-based justification to payers. Capturing the discussion of a diverse panel of clinicians, health care professionals, and scientists through the CGAC helps create strong, literature-based recommendations that allow for clear and concise letters of medical necessity and assist with peer-to-peer discussions with payers. Experience with this appeal process also allows the PMCS to help secure insurance approval for off-label use.

Finally, although the clinical consult notes are written primarily for the medical team, they also facilitate discussions directly with patients in the clinic. Rather than having a separate "personalized medicine clinic," PMCS has integrated these discussions into the routine care and clinic visits of each patient. A PMCS team member will coordinate with the attending oncologist to meet with the patient in the disease-specific clinic where the patient is usually seen.

Proactive Financial Considerations

Although the cost of genomic sequencing has declined rapidly in recent years, NGS is much more expensive than companion diagnostics for targeted therapies [23]. To provide large-scale somatic mutation testing that informs treatment decisions, hospitals must either make a substantial investment in equipment and Clinical Laboratory Improvement Amendments test development or contract with third-party providers. Still, the list price of sequencing can be as much as $7,200 per sample [24]. Many laboratories have decided not to bill patients or have charged significantly reduced prices for testing services, with the goal of generating clinical utility data and demonstrating sufficient value for payers to make favorable coverage and reimbursement decisions. This economic model is not sustainable in the long term, eventually requiring health systems, payers, patient, or some combination to be willing to pay for testing. Although sequencing is becoming a routine part of clinical care, research efforts to further drive down costs and increase quality will continue to be important.

The key to success for reference laboratories, patients, and payers is to accurately estimate the value provided by each test. In some cases, a more targeted genotyping approach may cost significantly less while still providing the majority of clinically actionable data compared with broader, whole-exome/genome testing. Patients with new diagnoses or in early stages of treatment may benefit most from smaller panels that would indicate appropriate targeted therapies or inform decisions

between standard-of-care options. Broad tumor sequencing is unlikely to alter first-line treatment regimens. Once patients have exhausted most or all standard-of-care options, large panels are then more likely to provide value by directing them to clinical trials or possible off-label use of approved drugs. However, this should be weighed against the availability of tissue. A reasonable argument for broader profiling at diagnosis can be made for cancers with tumors that are difficult to biopsy or have low tissue yields. Variants that are not actionable or informative may become so during the patient's natural history. Early use of NGS may require retesting as relevant mutations may have arisen during multiple cycles of therapy. Because of the high cost of these broad panels, serial retesting should be avoided when possible.

The emergence of so-called liquid biopsies allows for less invasive interrogation of patients' tumor mutation profiles by taking advantage of circulating tumor DNA in readily available body fluids such as plasma [25]. Liquid biopsies are poised to provide a sequencing option with distinct advantages to some of the challenges discussed previously. By using more abundant media, such as plasma or urine, as opposed to scarce tumor tissue, the issue of tissue availability is mitigated. However, the relative ease of procurement and clinical niche as a platform for detecting resistance mutations through serial sequencing at disease progression or therapeutic resistance increases the number of times a given patient may have their tumor sequenced, bringing a commensurate increase in sequencing cost.

Unnecessary costs should be contained to maximize patient benefit per dollar spent. However, it is important to recognize that the costs of genomic testing are relatively small compared with the total cost of treatment, particularly in complex diseases such as cancer. The tangible benefits of consumer-directed genomic testing can be debated, but the success of companies such as 23andMe demonstrates a willingness to pay for personal genomic information. Patients may thus be willing to bear the cost of testing to help direct therapy and make difficult treatment choices. Of course, economic analyses should be performed to objectively assess the value delivered for the cost based on the perspective of multiple payers.

Conclusion

As the treatment of cancer increasingly transcends the boundary between distinct site-of-origin based care and the shared genomic origins of disease [26], there has been great investment in bringing targeted molecular strategies to the patient. This transformation has spurred the molecular tumor board, a transdisciplinary approach that facilitates both the sharing of disease-specific expertise and the engagement of translational experts to shepherd precision cancer medicine into clinical practice. These teams will face complex challenges for which traditional evidence-based medicine decisions are not feasible. The tumor board must be prepared to objectively weigh evidence, while simultaneously accounting for patient-specific factors, to reach consensus decisions on the tumor genomic data. In the best of cases, these approaches will provide patients options where there were none and, done correctly, can lead to individual and societal advances in overall survival.

A critical need is the development of a relational clinical genomics database that can provide mechanisms to answer many of the questions posed above. By building collections of objective data on treatment selection and therapeutic response and the impact of particular variants, these databases possess the power to eventually turn the unknown into anecdotes, and anecdotes into verifiable data [27–29]. This will also provide objective data for payers to make reimbursement decisions. In the meantime, publicly available informatics resources are proving invaluable tools for assessment and translation of the novel into the familiar.

Automated systems will need to be developed to support teams as the volume of NGS results surpasses the burden that can be manually handled. These systems will identify cases in need of manual review, generate automated consults for cases that meet predefined criteria where manual review is not required, match patients to appropriate therapies and clinical trials, and aid in the curation of detected variants. Other information technology challenges, such as EHR integration and clinical decision support, exist and will require solutions that fit into the institutional information technology configuration.

Precision medicine approaches to cancer and immunotherapy have joined traditional chemotherapy, radiation therapy, and surgery as the pillars of cancer therapy. To successfully bring precision cancer medicine to patients, molecular tumor boards are critical tools capable of translating observed molecular alteration into clinical action and ultimately creating the pool of data for which future treatment standards will be set.

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