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Implementation and Outcomes of a Molecular Tumor Board at Herbert-Herman Cancer Center, Sparrow Hospital

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Objective. This paper describes our experience and outcomes from 54 cases presented to the (Molecular tumor board) MTB. **Methods.** 54 Cases presented between July 2017 and April 2018 were included in this analysis. These patients had different types of cancers that had either failed standard therapy or were expected to fail and physicians were looking for future options for anticipated progression. Patients who had obvious mutations and were candidates for Targeted Agent and Profiling Utilization Registry or Molecular Analysis for Treatment Choice clinical trials were not included. Oncologists presented the cases virtually and Foundation Medicine scientific and clinical team discussed the molecular pathways to find targeted options or trials. Tumor board attendees included oncologists, nurses, pharmacists, mid-level providers, residents and staff of the Cancer Center. **Results.** Amongst the 54 cases presented 81% had one or more potentially actionable alteration. 12 (22%) patients received genomically matched therapy as per MTB recommendations. Additional 13 (24%) patients have options available when they progress. Out of 12 patients who got treatment six are alive at the time of this analysis**.** Genomically matched therapy or Clinical Trials option were offered to the 46% of patients based on the MTB discussion. **Conclusion.** More widespread use of molecular diagnostics, better physician education and multidisciplinary collaboration between the staff involved in diagnosis and treatment, as well as third party payers are necessary for consensus on treatment and care of oncology patients.

Introduction

Precision medicine provides new options for cancer treatments and has become an integral part of oncology clinical practice. For some cancers, such as non-small cell lung cancer (NSCLC), precision medicine and genomic profiling is routinely used to integrate targeted treatments (1). Clinical trials with enrollment based on precision medicine have shown us the utility of targeted therapies to block specific molecular pathways activated in cancer (2-5). This is partly possible due to the availability of tumor genomic sequencing technology. These technologies have become more affordable and prevalent, which has led to increasing incorporation of next generation sequencing (NGS)-based comprehensive genomic profiling (CGP) in routine clinical practice. However, the use of CGP for treatment decision guidance is complex for oncologists as it often requires

complex interpretation of molecular biology and genomic results. With the increase in number of approved and investigational drugs, as well as the number of clinical trials incorporating the expanding knowledge of precision medicine, there is an increasing gap that needs to be filled.

Bridging this gap is largely possible in the setting of molecular tumor boards (MTBs). Multidisciplinary tumor boards in oncology are widely acceptable practice. MTBs include participants with a diverse spectrum of expertise and can provide guidance to oncologists seeking to implement such genomic-based personalized targeted therapy in practice (6-10). MTB review also serves as an educational tool, allowing for evidence-based interpretation of the genomic alterations found in each report. When supported by expert genomicists, bioinformatics specialists, pathologists and molecular oncologists, such discussions can provide rapid and accurate data analyses, comprehensive clinical assessment, as well as consideration of up-to-date availability of relevant clinical trials. Indeed, such MTBs are being established and successfully implemented for treatment decision support and for the guidance of optimal utilization of CGP in the clinic (6, 7, 9, 10).

This article describes the experience of a multidisciplinary MTB, which reviewed molecular profiling reports (Foundation Medicine, Cambridge, MA) of 54 advanced cancer patients with solid tumors who had exhausted or were likely to exhaust standard of care (SOC) options including available clinical trials at our own institution. All patients discussed at the Sparrow Hospital Herbert-Herman Cancer Center (HHCC) MTB between July 2017 and April 2018 are included in this analysis. The tumor board weighed evidence for actionability of genomic alterations identified by the molecular profiling and discussed possible treatment options.

Methods

The MTB at our cancer center was launched in July 2017 and met twice a month for 60 minutes each month in 2017 and then switched to once a month in 2018. The MTB comprised of medical and radiation oncologists, nursing, pharmacy and clinical trials staff from Sparrow Hospital, and was done virtually with the Foundation Medicine (FM) team including a genomicist and molecular oncologist. At each session four to five cases were presented and discussed in detail. These cases were referred by the treating oncologists. All information was de-identified in compliance with the Health insurance portability and accountability act (HIPAA). Patients and families were informed about the MTB decision making process when their case was referred for the discussion. The recommendations from the MTB were sent to each physician individually by email and maintained on the shared drive for future reference. This was discussed with the patients/families by the treating oncologist. If there was any change in treatment based on the MTB recommendation the new therapy was started only after the patients were educated by the nurses or pharmacist and patients were consented for the treatment.

The patient's treating physician or the senior oncologist, a clinical trials director, or a designated representative (e.g. physician assistant or Clinical trials specialist) presented the patient's case giving concise medical history including the date of diagnosis, type of tumor, therapies received and the relevant markers. This was followed by discussion from the FM genomics scientist and molecular oncologist of the molecular profiling results and implications for each case. Information discussed included the alterations detected in a given sample, their level of characterization and potential actionability. Targeted or immunotherapies

therapies matched to each alteration detected and approved in the patient's tumor type or in another tumor type, as well as openly enrolling genomically-matched clinical trials were also discussed. This was solely an advisory discussion. The ultimate decision to choose the therapy was left to the treating physicians.

Patients whose cases were selected for the MTB discussion had a range of different solid tumor types (n=53) or lymphoma (n=1). At the time of the MTB they had either failed standard therapy or were expected to fail and their physicians were looking for future options for anticipated progression. Patients who were obvious candidates for any of the open clinical trials at our site including the Targeted Agent and Profiling Utilization Registry (TAPUR) and the National Cancer Institute's Molecular Analysis for Treatment Choice (NCI-MATCH) Study were not selected for MTB discussion. Similarly, patients with clear matches to Food and Drug Administration (FDA) approved therapies in their tumor type were not selected for MTB discussion. Only the cases where the specific genomic mutation was not a direct match to an approved treatment or available clinical trial were selected for presentation to the MTB. By a direct match we meant if the patient's genomic mutation directly matched with the approved therapy. For example, if it was EGFR positive then treat with EGFR targeted treatment or if it was MSI high we will treat with FDA approved Immunotherapy. If after screening patients were eligible based on the genomic target to the list of available drugs on TAPUR or Match they would be enrolled on one of the clinical trials.

Hybrid capture-based comprehensive genomic profiling (Foundation Medicine, Cambridge, MA) was performed on 56 samples from 55 unique patients for 315 genes on submitted FFPE tissue samples (n=50), for 405 genes on whole blood (n=3), or for 62 genes on circulating tumor DNA isolated from submitted blood samples (n=3) as previously described (11-13). Most of the patients were sent for genomics when they progressed. However, if it was not possible to get fresh tissue, archival tissue was used from the initial diagnosis. Genomic alterations including base substitutions, insertions/deletions, copy number changes, and rearrangements were assessed, as well as determination of tumor mutational burden (TMB) and microsatellite instability (MSI) status (14, 15).

Results

Patient Characteristics

Patients presented from July 2017 to April 2018 were included in this analysis. CGP results for a total of 55 patients were presented for MTB discussions. One patient discussed in the MTB had lymphadenopathy only and did not have cancer so was excluded from analysis. All other patients (n = 54) were heavily pretreated advanced cancer patients who had exhausted or were likely to exhaust SOC options including available clinical trials at our own institution. Only those patients whose oncologist could not easily identify an appropriate genomically-matched treatment option from the CGP report and thus required the knowledge of the genomics and bioinformatics team were selected for MTB discussion (Figure 1).

Among the tumor types presented the majority of cases were gynecological malignancies (28%, 15/54) followed by breast carcinoma (17%, 9/54), colorectal carcinoma (9%, 5/54), non-small cell lung carcinoma (9%, 5/54), or other tumor types (37%, 20/54).

Demographics of the patients discussed are represented in Table 1. Median age was 64 years (range 37-82) and 69% (37/54) were females. Patients discussed at this MTB had an average of 2.4 prior lines of therapy be-

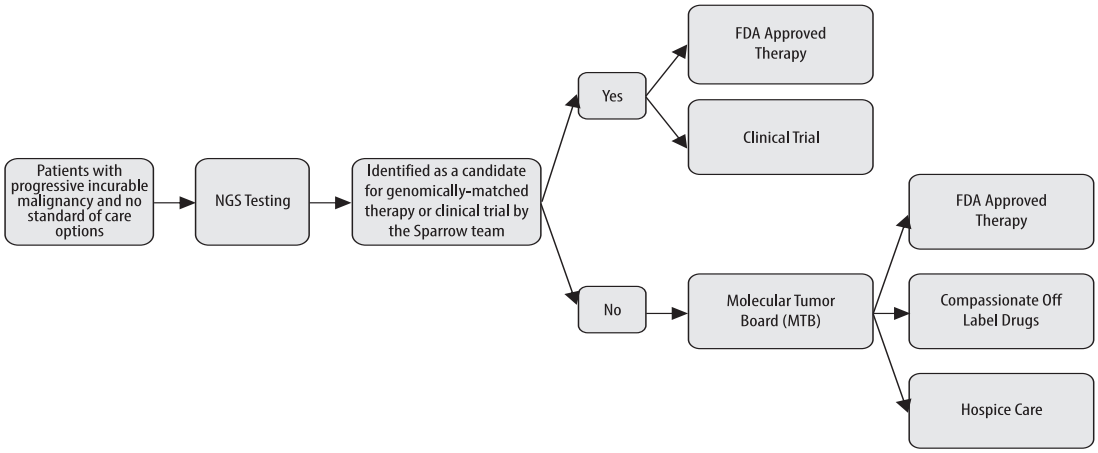

Figure 1. Flow chart depicting selection of patient cases for the Sparrow Health MTB and resulting treatment options.

Table 1. Patient Demographics and Disease History

Demographics	MTB Patients (%)
No. patients	54
Median Age (years)	64
≥65 years	26 (47)
<65 years	28 (53)
Gender (Male:Female)	17 (31):37 (69)
Disease histology	
Gynecological	15 (28)
Breast	9 (17)
NSCLC	5 (9)
CRC	5 (9)
Other	20 (38)
Number of prior lines of therapy	
Mean	2.39
Median	2
1 line	14 (26)
2 lines	18 (33)
3 lines	14 (26)
4 lines	5 (9)
5 lines	1 (2)
6 lines	2 (4)

MTB=Molecular tumor board; NSCLC=Non-small cell lung cancer; CRC=Colorectal cancer.

fore CGP was performed; 74% (40/54) of patients had received ≥1 line of therapy and 15% (8/54) of patients received ≥ 3 lines of prior therapies. At the time of analysis 32 patients (59%) were still alive.

Genomic Alterations and Potential Treatment Options Identified

Of the 54 total patients, 100% had potentially actionable alteration(s) identified by CGP. An actionable alteration is defined by being linked as either a positive or negative biomarker for an approved therapy or enrollment criteria for an open clinical trial. (Personal communication) Thirteen patients (24%) had alterations with matched therapy in their tumor type, 25 patients (46%) had alterations with matched therapy in another tumor type, and 16 patients (30%) were identified with alterations with a genomically matched clinical trial options (Figure 2). In 76% (41/54) of cases, more than one potentially actionable alteration was identified.

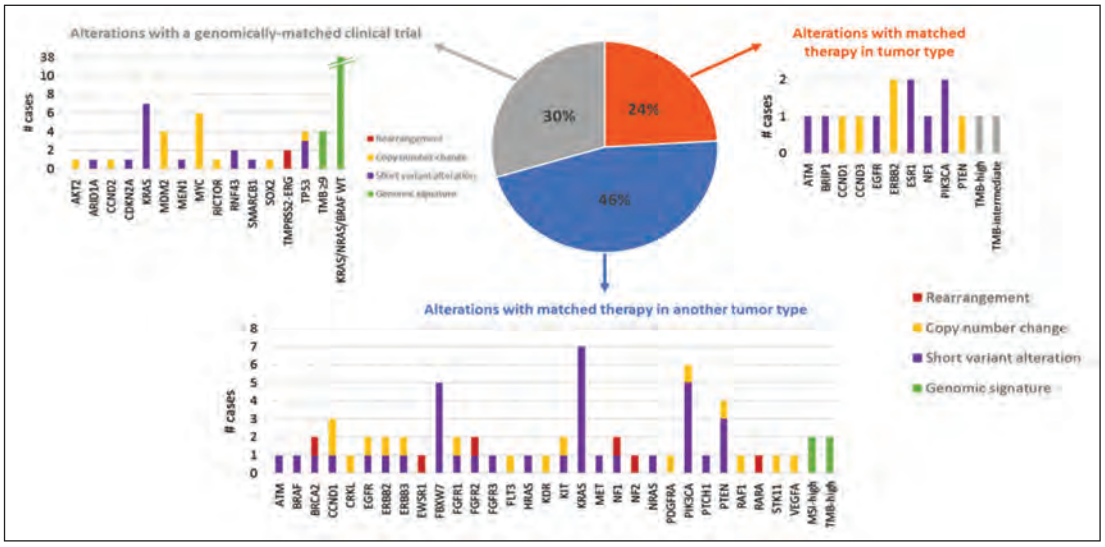

Figure 2. Distribution of potentially actionable alterations identified using CGP. Actionability was assessed at the time of reporting for a given case. Note: a therapy may be approved in a patient's tumor type, but the patient still may not qualify for the therapy based on the specific FDA label. TMB ≥9 mutations/Mb is used as a designator for clinical trial eligibility specifically due to the enrollment criteria for the TAPUR trial pembrolizumab arm, which was open at the time of this study. TMB-intermediate and TMD-high designations for therapy associations were made by Foundation Medicine.

The distribution of potentially actionable alterations identified is shown in Figure 2.

Treatment Assignments and Patient Outcomes

We further analyzed how MTB discussions influenced the implementation of treatments in our patients. Twelve (22%) patients received a genomically-matched therapy based on CGP results and MTB discussion (Table 2). Of note, 2 patients received what was assessed to be a genomically-matched treatment based on MTB discussion and the treating physician's discretion, but the therapy received was not listed on the CGP report (Table 2, patients 8 and 11). Out of these 12 patients, 9 had stable disease (SD) as their best response to matched therapy, and 3 had progressive disease (PD) as assessed by recist 1.1 criteria. At the time of follow-up 9 had progressed and 3 maintained SD. The median follow-up period was 17 months. Patients who eventually progressed stayed on treatments between 3 and 15 months. Average time to progression was 7.6 months. Six out of 8 patients who had progressed were alive at the time of analysis (median time to follow up=17 months). An additional 13/54 (24%) patients are anticipated to receive matched treatment options when they progress on current SOC therapy.

Five out of 54 (9%) patients had at least one potential genomically-matched therapy option identified, but we could not get approval from insurance (n=4) or the patient did not qualify for available trial(s) primarily due to poor performance status (n=1). Three patients received treatment on label as recommended by MTB. The treating physician did not recognize the direct match and referred to the MTB and the tumor board discussed and recognized the match to the therapies. If those patients were not presented at MTB they would not have gotten these therapies. Six patients (11%) had genomically-matched options available, but the treating physician chose a different option. This was due to other available agents judged to be more effective than targeted

Table 2. Clinical and Genomic Characteristics of Patients' Treatment Based on MTB Discussion

Patient	Diagnosis	Matched alteration	Matched targeted therapy	PFS (months)	Best Response
1	Anus SCC	KRAS/NRAS/ BRAF WT	Cetuximab on trial	15	PD
2	Uterus Endometrial Adeno	ERBB2 amplification	Trastuzumab on clinical trial	6	SD
3	Ovary granulosa cell tumor	CDKN2A p16INK4a A60fs*89	Palbociclib on trial	3	PD
4	Ovary serous carcinoma	ATM D2721M	Olaparib (FDA-approved on-label)	SD	SD
5	Breast carcinoma (NOS)	BRCA2 V1988I	Olaparib (FDA-approved off-label)	8	SD
6	Lung adenocarcinoma	EGFR exon 19 del + T790M	Osimertinib (FDA-approved on-label)	SD	SD
7	Lung SCC	KRAS/NRAS/BRAF WT	Cetuximab on trial	4	PD
8	Adrenal gland cortical	FGFR2-CIT fusion	Sunitinib on trial*	5	SD
9	Breast ILC	ESR1 Y537N	Fulvestrant on label	10	SD
10	Ovary serous carcinoma	MSI-H and TMB 19 mutations/Mb	Pembrolizumab on trial	12	SD
11	Colon Adenocarcinoma	TMB 8 mutations/Mb	Pembrolizumab off label†	SD	SD
12	Breast carcinoma (NOS)	CCND1 amplification	Palbociclib on label	5	SD

MTB=Molecular tumor board; PFS=Progression free survival; SCC=Squamous cell carcinoma; WT=Wild Type; PD=Progressive disease; SD=Stable disease; NOS=Not otherwise specified; ILC=Invasive lobular carcinoma; MSI-H=Microsatellite instability high; TMB=Tumor mutational burden; Mb=Megabase. *This patient was approved for the sunitinib arm of the TAPUR trial based on the FGFR2-CIT fusion alteration detected; however, sunitinib was not one of the matched therapies listed on the CGP report. †This patient was approved for insurance coverage of off label pembrolizumab based on MTB discussion and TMB of 8 mutations/Mb; however, pembrolizumab was not listed as one of the matched therapies on the CGP report.

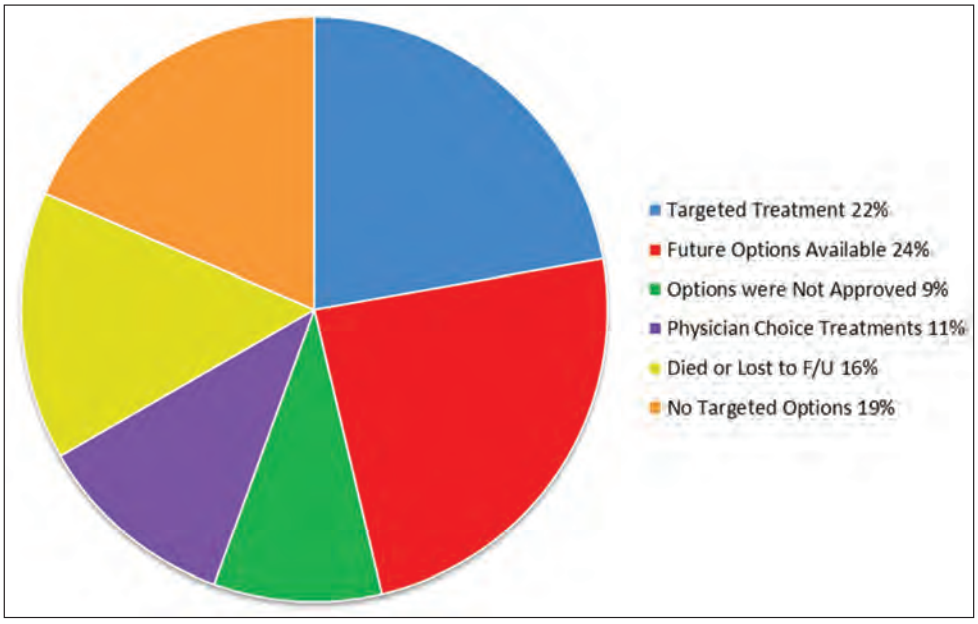

Figure 3. Patient Treatment Assignments Based on Molecular Tumor Board Discussions.

therapy or inability of the patient to travel to far away sites for treatments. Eight patients (16%) either died prior to planned treatment or refused further treatments. One patient was lost to follow up and ten patients (19%) did not have targetable options, even though they had mutations (Figure 3). In total, a genomically matched therapy or clinical trial option was able to be offered to the patient in 81% (44/54) of cases based on the MTB discussion.

Discussion

There is an increasing body of evidence based on prospective and retrospective studies, case reports, and clinical practice showing that matching targeted agents with genomic alterations improves patient outcomes (16). Clinical reports suggest that 30%-80% of advanced solid tumors harbor potentially actionable genomic variants (17). Meta-analysis of 570 Phase II studies of new anticancer agents, done on 32,149 patients showed that personalized approach correlated with statistically significant higher median responses rates, prolonged median progression free survival and improved overall survival (18). Additional Meta analyses by Schwaederle M et al. also demonstrated benefit for patients treated with personalized matched therapy (19, 20). Prospective molecular profiling studies by Stockley et al. demonstrated that treatment with genotype matching in early phase was associated with an increased objective tumor response (13). Wheeler et al. reported that use of CGP to assign therapies in patients with multiple genomic aberrations was associated with longer time to treatment failure and stable disease in patients with refractory malignancies (21). In the multicenter open label phase 2 trial (SHIVA) authors showed that molecularly targeted agents did not improve significantly medium progression free survival (PFS) when compared to physicians' choice of treatment. However, there was a signal for very slight improvement in the PFS, 2.3 versus 2 month in experimental group vs. the control group. This French trial limited molecular alterations to ones identified within 3 molecular pathways (hormone receptor, PI3K/AKT/mTOR, RAF/MEK) which is the limitation of this study (22).

Another prospective trial, emulating clinical benefits of high throughput genomic analysis in clinical practice, MOSCATO – 01 showed that high throughput genomics could improve outcomes in a subset of patients with hard-to-treat cancers. Although only 7% of successfully screened patients benefited from this approach, we think that with the further refinement of this approach higher or larger number of patients will benefit (23).

However, implementation of genomic-based precision medicine in oncology represents major challenge due to depth of knowledge and expertise required to make decisions which will benefit patients. Obstacles to implementation of precision medicine in clinical practice are particularly high in community practices. They include time-consuming analyses of results of molecular testing, determining clinical trial eligibility, molecular test selection, determining the optimal time for molecular testing, financial concerns, genetic counseling and particularly patient attitudes. MTBs overcome some of those obstacles by providing necessary expertise in a multidisciplinary setting. The MTB at HHCC was established in July 2017 as cooperative multidisciplinary board in association with FM and in a short period showed to be of great benefit for our patients. We found targetable non-KRAS alterations in 81% of cases. This is similar to results reported by other molecular tumor boards (39-86%) (10, 24, 25). These percentages depend upon definition of actionable alterations, and are sensitive to selection bias, since it is expected that physicians will most often

submit cases for discussion at MTBs they believe have potentially actionable alterations detected by CGP. With advancement in standardization of variant calling and reporting we can expect that differences and biases will be reduced and results from different studies will become more comparable. In the case of our MTB, patients were selected when they did not have a clear choice for a genomically-matched clinical trial open at HHCC and did not have a direct match to an approved targeted therapy. However, we also discussed and recommended future treatments for patients who were still stable or responding to present treatment. This may be specific for our MTB and could skew results toward higher numbers.

Patients treated based on recommendations from our MTB (n=12) benefited from treatment and those who ultimately progressed (n=9) stayed on treatments between 3 and 15 months (mean 7.6 months). Mean progression free survival on the prior therapy for these patients (n=9) was 4 months. Six out of 8 patients who eventually progressed were still alive at the time of analysis. An additional 3 patients are still being treated with matched therapy and have Stable disease (SD). All these patients had very advanced disease and the only other option was symptom control and Hospice. Data from 126,620 patients extracted from the electronic medical records of 10 hospices in the CHOICE network (Coalition of Hospices Organized to Investigate Comparative Effectiveness) showed that 93.6% of those patients died within 6 months (26).

One of the characteristics of our MTB was that 13/54 patients were still responding or were stable on previous treatment at the time of the MTB. NGS testing in these patients was done mostly due to patients', families' and physician's anxiety and need to have other available options. Similar observations were made by Schwaederlea et al. and could be considered as a limitation related to the current use of molecular diagnostics. The authors believe that early, and maybe premature testing is related to the time to obtain results (in their case median of 27 days). Consequently, physicians are ordering tests before patients have failed previous treatment (8). In the case of our patients all 13 have potential molecular targets identified by CGP when they progress. We expect that with better and more efficient work flow between local pathology and molecular diagnostic companies' time to obtain results will be significantly reduced and delays will be eliminated. That will taper patients' and physicians' anxiety and bring more appropriate timing of testing.

One of the main concerns from analysis of our MTB results was that 6/54 patients had available molecular targets, but were still treated with chemotherapy by their treating physicians. In addition, 8/54 patients refused recommended molecular treatment or died before it could be applied. Patient's refusal at least partially can be explained by physician's hesitance to use molecular targeted therapy. This is not unexpected since most of the presently practicing oncologists are trained in the era of the "evidence-based medicine" and use of cytotoxic chemotherapy. Although far more informative and accurate than its predecessors of intuition and the "art of medicine", the unfortunate consequence of the approach of "evidence-based medicine" is that outliers are not represented, and they may be unlikely to respond similarly to the average patient for any given treatment. Precision or personalized medicine, in contrast, focuses on the individuals and seeks to improve health outcomes by integrating a huge variety and number of data points, from genomics to environmental and lifestyle factors, in order to provide an individualized approach to health care (27). Although molecular diagnostics use and practice at HHCC is considered advanced, it is still necessary to improve education and

participation of all treating physicians. MTBs by their structure represent ideal vessels for education, collegiate interaction, multidisciplinary discussion and finally creation of consensus on treatment and care of patients. However, they require full participation of and interaction between all involved participants. Otherwise, opportunities will be missed. There are definite obstacles that need to be overcome, in particular limited available time, especially in busy practices where physicians' income is based on number of patients seen. In order to resolve this important issue, it is necessary to have better understanding of precision medicine by policy makers, third-party payers, hospital administrations, patients and the general public. Development of clinical decision algorithms based on molecular testing and available targeted therapies will make resolution easier. Expected results from precision medicine trials including the National Cancer Institute NCI-MATCH and IMPACT (1-3), and ASCO-TAPUR (17) could help to clarify the role of precision medicine and consequently MTBs in the every day s care of oncology patients.

Need for education and collaboration between providers and third-party payers is emphasized by the number of patients who had molecular targeted options identified, but were refused treatment coverage by payers (n=4), as well as patients who refused treatment (8/54). The main reason for these decisions are, in our opinion, costs of the medications, out-of-pocket costs for patients and/or overall costs for third party payers. Bryce et al. (28) had similar experience with their patients at a Mayo MTB where 6% of the patients with targetable mutations were not able to receive targeted therapy due to insurance denying payments. Hopefully, the increasing trend to incorporate molecular testing and targeted therapy into National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines will facilitate approval in these cases. It is also our recent experience that some, but not all, third party payers are more inclined to approve targeted therapy based on valid molecular testing.

In 10/54 cases patients did not have targetable options as assessed by the MTB. In these cases therapy or trials were identified linked to a KRAS mutation only (low level of evidence for efficacy) and none of these patients received genomically matched therapy. In 1 additional case the only "genomic match" for actionability was not a directly targetable alteration, but rather option for the KRAS/NRAS/BRAF wild type (WT) cetuximab TAPUR arm. These data argue that CGP identifies potentially actionable alterations in a large majority of patients, but more published evidence for genomically-matched targeted therapy, better access to drugs and trials, more investment into education, better collaboration between all parties vested into patients' care and possibly more appropriate timing of NGS testing (so patients do not die before getting treatment) is needed.

Conclusion

The MTB is multidisciplinary platform for discussion, treatment recommendations and knowledge acquisition related to genomic testing and precision oncology. Although precision medicine is progressing in breathtaking pace, practice of MTB's is lagging behind. In most of the cases it is limited to large Academic centers. This paper presents model of collaboration between community cancer center and sophisticated technology company that ultimately improves oncology patients' care. This model can be used, with local modifications, in other community centers and bring advantages of precision medicine to more than 80% of all oncology patients, who are treated in their local communities.

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Conflict of Interest: Dr. Srkalovic is on the speakers bureau of Foundation Medicine. None of the other authors have declared any conflict of interest associated with this work.

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