The Journal of Molecular Diagnostics, Vol. 17, No. 6, November 2015

ELSEVIER

the Journal of Molecular Diagnostics

jmd.amjpathol.org

Development of a Center for Personalized Cancer Care at a Regional Cancer Center

Feasibility Trial of an Institutional Tumor Sequencing Advisory Board

Brian R. Lane,[*†‡§] Jeffrey Bissonnette,[¶] Tracy Waldherr,[‖] Deborah Ritz-Holland,[‖] Dave Chesla,[**] Sandra L. Cottingham,[*,**†††] Sheryl Alberta,[¶] Cong Liu,[¶] Amanda B. Thompson,[¶] Carrie Graveel,[‡] Jeffrey P. MacKeigan,[‡] Sabrina L. Noyes,[*§] Judy Smith,[*†‡‡] Nehal Lakhani,[*§§] and Matthew R. Steensma[*†‡¶¶], for the Spectrum Health Tumor Sequencing Advisory Board

From the Spectrum Health Cancer Center, the Division of Urology,[§] the Advanced Technology Laboratory,[¶] Molecular Diagnostics, the Office of Clinical Research Operations,[‖] the Spectrum Health Universal Biorepository,** and the Departments of Pathology,[††] Oncology,[‡‡] and Orthopaedic Oncology,[¶¶] Spectrum Health System, Grand Rapids; the Department of Surgery,[†] Michigan State University College of Human Medicine, Grand Rapids; the Center for Cancer and Cell Biology,[‡] Van Andel Research Institute, Grand Rapids; and the Department of Hematology/Oncology,[§§] Cancer and Hematology Centers of West Michigan, Grand Rapids, Michigan*

Accepted for publication July 1, 2015.

Address correspondence to Brian R. Lane, M.D., Ph.D., Spectrum Health Medical Group, 4069 Lake Dr., Ste. 313, MC 9016, Grand Rapids, MI 49546. E-mail: brian.lane@spectrumhealth.org.

Next-generation sequencing (NGS) capabilities can affect therapeutic decisions in patients with complex, advanced, or refractory cancer. We report the feasibility of a tumor sequencing advisory board at a regional cancer center. Specimens were analyzed for approximately 2800 mutations in 50 genes. Outcomes of interest included tumor sequencing advisory board function and processes, timely discussion of results, and proportion of reports having potentially actionable mutations. NGS results were successfully generated for 15 patients, with median time from tissue processing to reporting of 11.6 days (range, 5 to 21 days), and presented at a biweekly multidisciplinary tumor sequencing advisory board. Attendance averaged 19 participants (range, 12 to 24) at 20 days after patient enrollment (range, 10 to 30 days). Twenty-seven (range, 1 to 4 per patient) potentially actionable mutations were detected in 11 of 15 patients: *TP53* ($n = 6$), *KRAS* ($n = 4$), *MET* ($n = 3$), *APC* ($n = 3$), *CDKN2A* ($n = 2$), *PTEN* ($n = 2$), *PIK3CA*, *FLT3*, *NRAS*, *VHL*, *BRAF*, *SMAD4*, and *ATM*. The Hotspot Panel is now offered as a clinically available test at our institution. NGS results can be obtained by in-house high-throughput sequencing and reviewed in a multidisciplinary tumor sequencing advisory board in a clinically relevant manner. The essential components of a center for personalized cancer care can support clinical decisions outside the university. *(J Mol Diagn 2015, 17: 695—704; http://dx.doi.org/10.1016/j.jmoldx.2015.07.003)*

The landscape of cancer care is evolving because of the increased availability of biomarker information that defines each individual's cancer.[1,2] Although current models of care incorporate infrastructure and information to enable individual providers and patients to pursue a treatment plan, the complexity of these plans continues to increase.[2] Decades of research have identified numerous biomarkers with predictive and/or prognostic significance for various cancer types.[3] The first, and perhaps best, example of such personalized cancer care is the ability to cure acute promyelocytic leukemia with the combination of all-trans-retinoic acid and arsenic trioxide based on the identification of the PML/RAR-α fusion protein as the driver event.[4,5] Subsequently, the 73.7% clinical response rate to the epidermal growth factor receptor (EGFR) inhibitor gefitinib (versus 30.7% with standard chemotherapy) for the 10% of non—small cell lung cancers harboring *EGFR*

Supported by grants ORCM.FY14.01 and ORCM.FY15.02 (B.R.L.) from the Spectrum Health Cancer Program Internal Grant Initiative Committee.

Disclosures: None declared.

The members of the Spectrum Health Tumor Sequencing Advisory Board are listed in the Acknowledgments.

http://dx.doi.org/10.1016/j.jmoldx.2015.07.003

mutations and the 63% relative reduction in the risk of death with vemurafenib for malignant melanoma patients with *BRAF* mutations are notable 21st-century examples.[6–9] Although there are individual biomarker tests for several disease states, limitations include the time required for sequential testing and tissue needs for multiple tests.

Next-generation sequencing (NGS) capabilities have expanded such that generating a comprehensive, individual mutational landscape in real time appears feasible in research settings.[10–12] Early efforts at major academic centers suggest personalized cancer care can be delivered; however, substantial institutional resources are required.[2,10,13] With most cancer care in the United States delivered outside the university setting, it remains to be determined whether patients receiving care in the community will be able to benefit from these advances. Recently, with commercially available platforms and assays to perform NGS in Clinical Laboratory Improvement Amendments (CLIA) environments, NGS testing can be performed at a wider number of centers outside university and/or research settings.[14,15] Several questions remain regarding the feasibility of providing personalized cancer care using NGS results in nonuniversity cancer centers, where most patients receive their care.[16–19] Although the cost and availability of multiplex assays are becoming less problematic, the integration of such testing into clinical care has largely been left up to the treating physician.

The complexity of cancer care is expanding exponentially. New molecular alterations, compounds, and clinical trials are discovered on a weekly basis. There is great variability in comfort of cancer specialists with molecular information.[19,20] Even for those comfortable leveraging this information, there remain huge gaps in the available data regarding matching mutations to treatments, and a pairing that leads to effective treatment for one cancer type does not ensure success for other cancer types. In their initial personalized care efforts, major university centers have convened molecular tumor boards that include broad participation of clinical experts, translational scientists, and others.[2,10,13] Whether such processes can be paralleled at a regional cancer center is currently unknown. We report the results of a pilot clinical trial exploring the feasibility of convening an institutional, multispecialty tumor sequencing advisory board (TSAB) to evaluate NGS results obtained within a CLIA-approved laboratory. Specifically, we outline the roles, function, and interaction of a multidisciplinary TSAB.

Materials and Methods

Study Design

The Spectrum Health Universal Biorepository enrolls patients undergoing surgery for suspected malignant tumors within an institutional review board (IRB)–approved framework (IRB 2011-332). From September 1, 2013, through January 20, 2014, a total of 361 patients were enrolled in the Spectrum Health Universal Biorepository. The initial screening process for this trial sought patients with treatment-refractory cancers; however, during the clinical trial screening by TSAB coordinators, criteria were expanded to also identify patients with advanced cancers without standard treatment options (IRB 2013-031). Of 361 patients, 340 were excluded due to low-risk cancer ($n = 191$) or inadequate tissue ($n = 149$), leaving 21 patients who met the entry criteria (Figure 1). Of these 21 patients, six were excluded based on low percentage of tumor nuclei (<60%) by histologic review. The resulting 15 patients made up the study population for this trial. Under IRB approval (IRB 2013-031), patients with advanced or treatment-refractory cancer were approached to provide signed informed consent if they met inclusion criteria. Patients who were non–English-speaking, <18 years of age, pregnant, or prisoners were excluded. Tumor tissue was required for molecular sequencing, either from a previously collected formalin-fixed, paraffin-embedded (FFPE) block or from fresh tumor tissue being collected as part of standard of care.

Specimen Processing

Tumor specimens were obtained from either fresh frozen or FFPE samples with controlled fixation durations (<72 hours). Initial criteria were for 75% tumor nuclei; however, this excluded cases that were deemed adequate by the participating pathologists. When the sample obtained for research did not meet these criteria, surgical blocks were reviewed for potential additional tissue in adherence with College of American Pathologists guidelines. Samples with lesser tumor content were annotated for tumor macrodissection. Those unable to be macrodissected were excluded from further consideration. Therefore, during the trial, the initial criteria were modified to allow for samples with lower tumor nuclei content if a larger amount of tissue was available. The final pathologic criteria considered sufficient for processing were as follows: i) the sample size must be at least 100 mg with at least 60% tumor nuclei for fresh tissue, ii) FFPE samples that were ≥5 mm needed 60% tumor nuclei or 80% if ≤3 mm in thickness, and iii) samples with mucinous or inflammatory component were compared with the slides and FFPE samples from the surgical case to determine the best candidate sample.

NGS Technology

DNA from the tumor specimens was extracted. Targeted amplification was performed using the Ion Torrent Cancer Hotspot Panel version 2 (CHPv2; Life Technologies, Carlsbad, CA), which is designed to detect common mutations in target regions, including approximately 2800 COSMIC (Catalogue of Somatic Mutations in Cancer) mutations from the following 50 oncogenes and tumor suppressor genes: *ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAS, GNAQ, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53,* and