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Pre-Appointment Testing for *BRAF/KIT* Mutation in Advanced Melanoma: A Model in Molecular Data Delivery for Individualized Medicine

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Abstract

The emergence of individualized medicine is driven by developments in precision diagnostics, epitomized by molecular testing. Because treatment decisions are being made based on such molecular data, data management is gaining major importance. Among data management challenges, creating workflow solutions for timely delivery of molecular data has become pivotal. This study aims to design and implement a scalable process that permits pre-appointment *BRAF/KIT* mutation analysis in melanoma patients, allowing molecular results necessary for treatment plans to be available before the patient's appointment. Process implementation aims to provide a model for efficient molecular data delivery for individualized medicine. We examined the existing process of *BRAF/KIT* testing in melanoma patients visiting our institution for oncology consultation. We created five working groups, each designing a specific segment of an alternative process that would allow pre-appointment *BRAF/KIT* testing and delivery of results. Data was captured and analyzed to evaluate the success of the alternative process. Over one year, 35 of 55 (59%) patients had prior *BRAF/KIT* testing. The remaining 20 patients went through the new process of pre-appointment testing; results were available at the time of appointment for 12 patients (overall pre-appointment results availability = 85.5%). The overall process averaged 13.4 ± 4.7 days. In conclusion, we describe successful implementation of a scalable workflow solution that permits pre-appointment *BRAF/KIT* mutation analysis and result delivery in melanoma patients. This sets the stage for further applications of this model to other conditions, answering an increasing demand for robust delivery of molecular data for individualized medicine.

Keywords

BRAF; *KIT*; melanoma; pre-appointment testing; workflow solutions

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Introduction

Individualized medicine, the anticipated paradigm for future healthcare, is an attempt to optimize therapy for an individual patient while increasing effectiveness and decreasing side effects and cost. The 3 cornerstones of this approach are pharmacogenomics [1-3], cellular/genetic bioengineering [4, 5], and precision diagnostics [6]. Precision diagnostics requires timely delivery of multidimensional and high-throughput data streams to healthcare providers in order to make therapeutic decisions [7, 8]. In recent years, incorporating results of molecular testing in this data has become essential [9, 10]; workflow solutions have become necessary to address this emerging need.

We selected *BRAF* and *KIT* mutation testing in advanced stage melanoma as a model to develop a scalable process that ensures timely delivery of molecular data required for targeted therapy decisions. Melanomas with *KIT* mutations can benefit from imatinib and other *KIT* inhibitors [11]. More importantly, the recent Food and Drug Administration (FDA) approval and survival benefits of the *BRAF* inhibitor vemurafenib (with the prospect of other drugs in the pipeline), requiring *BRAF* V600E testing for its use in advanced melanoma, has produced a need to have the *BRAF* mutational status available at the time of the patient's appointment with the oncologist in order to plan chemotherapy [12]. Hence, identifying the patient's *BRAF* and *KIT* mutational status has become critical in devising treatment plans for patients with advanced melanoma. We sought to replace the original process, in which *BRAF* and *KIT* testing was initiated following the patient's appointment, creating a significant delay in treatment decisions, with a process that would ensure delivery of *BRAF* and *KIT* mutation results at the time of the appointment. Our choice of melanoma as a model in molecular data delivery for individualized medicine was made because of the limited number of care providers involved at our institution and the relatively small number of patients, allowing testing of an easily scalable process using a small pilot group.

This study aims to examine the existing workflow of *BRAF* and *KIT* testing in advanced melanoma, and if necessary, replace it by a new more efficient process that is both scalable and efficient, allowing for molecular data delivery at the time of the patient's appointment. Scalability will allow monitoring of success of the new process and will permit the melanoma model to serve as a pilot for pre-appointment molecular data deliver for individualized medicine, with the potential of benefiting an increasingly large number of neoplastic and non-neoplastic diseases.

Materials and Methods

Existing process

Proposing an alternative process requires examining the existing workflow (figure-1). In the old process, upon arrival of the patient with his/her material, the slides are routinely reviewed by our anatomic pathologists to confirm the outside diagnosis. This occurs in a special service at the division of anatomic pathology (AP) designated "Mayo Clinic 3" (MC3). *BRAF* and *KIT* testing, ordered after the appointment in the old process, are performed at two different labs: Molecular Genetics (MolGen) lab and Molecular Anatomic Pathology (MAP) lab, respectively. Once molecular testing is completed, the results are

released into the patient's electronic medical records; while results from the MolGen lab are released directly into the MICS (Mayo Integrated Clinical Systems) electronic medical record system, MAP results reach the system through CoPath. This process takes up to several weeks after the patient's appointment. During this time, the patient either waits in a hotel, is admitted at the hospital (if critically ill), or returns home until the results are available, at which time a treatment plan can be devised. This delay in delivering a treatment plan incurs unnecessary cost, negatively impacts patient satisfaction, decreases efficiency of physicians, and potentially affects the patient's well-being (if critically ill).

Medical oncology scheduling / patient correspondence system

In the original process, phone calls from patients calling our institution to make an appointment for their melanoma care are handled by professional patient appointment coordinators operating according to well-delineated and regularly updated scripts. Utilizing scheduling criteria provided by their division, coordinators determine the urgency of the appointment and choose the appointment date accordingly. Most appointments are scheduled within 2 to 3 weeks of the patient's phone call.

PCS, a system based on Adobe Live Cycle and Flex applications, is a comprehensive communications management tool linked to the Mayo Scheduling System (MSS) that supports the creation of patient appointment and business office correspondence. PCS allows simplified management of high-volume appointment through improved template maintenance. This assists in standardizing messages and minimizing errors while enhancing patient confidentiality and providing a clear audit trail. PCS routinely mails incoming patients an appointment guide, which contains the listing of appointment times, locations, and routine lab testing instructions.

Molecular testing

Material used for molecular testing is handled by cytotechnologists and trained medical secretaries; material related data is routinely recorded and tracked in a spreadsheet located in the AP server. For *BRAF* mutation testing, DNA is extracted from 10 µm thick sections of FFPE tissue using a standard protocol on the Qiacube extraction platform (Qiagen, Valencia CA). The lab developed test for *BRAF* is an allele specific PCR with fragment analysis by capillary electrophoresis that is designed to detect the V600E alteration only. For *KIT* mutation testing, DNA is extracted from 5 µm thick sections of FFPE tissue using a phenol/chloroform method for small tissues, or a column-based method for larger tissues. *KIT* mutational status is determined by polymerase chain reaction (PCR) and gene sequencing for the detection of mutations in the Homo sapiens v-KIT Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*) exons 11, 13 and 17 using GeneAmp PCR System 9700 (Thermal Cycler) according to the manufacturer's instructions.

Working groups

In order to devise and execute an alternative process, the following 5 working groups were created:

- MOS group: oversees the initial communication with the patient for scheduling an appointment with medical oncology. This group also ensures transfer of necessary patient and appointment information to the AP group (see below) for timely initiation of molecular testing.
- PCS group: manages pre-appointment communication with the patient via postal service following the initial patient communication with MOS.
- Anatomic pathology (AP) group: manages identification, requisition, securing, and initial handling of patient material for diagnosis confirmation and initiation of molecular testing.
- MolGen/MAP group: optimizes the pre-test processing of patient samples and manages *BRAF* and *KIT* molecular testing.
- Pathology informatics/project oversight group: identifies key checkpoints in the workflow process for data capturing, and collects and analyzes data utilizing Microsoft Access software. The data is used to determine success for the overall project goal and identify problem points in the process.

Each group held monthly meetings to identify points of delay in the existing process, devise scalable alternatives, and ensure that these alternatives were implemented. Once solutions were devised for every step in the process from the time of the patient's phone call to the time of making a treatment decision, we set to implement the new workflow and monitoring system in a trial period of 1 year. During this time 55 new patients went through the process. The primary metric was the number of patients for which the *BRAF/KIT* results were available to the clinician at time of initial visit. Our goal was a minimum pre-appointment availability of *BRAF* results of 80%.

Change in *BRAF* testing method

FDA approval of the COBAS® *BRAF* test from Roche and implementation of this test overlapped the development and implementation of the alternative process. The FDA approved COBAS® 4800 *BRAF* V600 mutation test was performed per manufacturer's instructions on melanoma samples only and was initiated 3 months following implementation of the alternative process.

Results

The original workflow was replaced by an alternative process summarized in figure-2. In order to realize this novel process, the following changes had to be implemented in each working group:

Medical oncology scheduling group

Figure-3 delineates the steps involved in segment-1 of the process. In order to initiate testing prior to the patient's arrival at our institution, an "Authorization to Release Protected Health Information" must be obtained; this allows access to the patient's material prior to the appointment. It can be sent to the patient by email, fax, or postal service; the faster modes of communication were preferred to allow the earliest possible access to patient material. An

accompanying explanatory letter was also designed to be sent along with the release form providing instructions on how to complete the form and send it back to our institution.

A script and standard Operation Procedures (SOPs) were developed to guide the MOS team during their phone discussion of the pre-appointment molecular testing with the patient. The script also instructs the appointment coordinator to ask the patient whether or not he/she was previously tested for *BRAF* or *KIT* mutation. Finally, a unique identifying cover letter differentiating melanoma cases from other cases was designed. Once the completed release form is received from the patient, it is faxed along with the cover letter from the appointment coordinator to the AP medical secretaries. The cover letter flags cases that must undergo pre-appointment *BRAF/KIT* testing, thus ensuring the continuity of the process as it transitions from the MOS to the AP group. Data from this segment of the process was captured by the pathology informatics/project oversight group (table-1).

Patient correspondence system group

In the process design, fax and email communications were to be handled by MOS whereas postal communication was to be handled by PCS; the possibility of mail automation and fast mail dispatch provided by PCS would allow for both the scalability and efficiency desired in the process. However, during process implementation, the PCS was undergoing a transition in information technology, moving from General Patient Appointment System (GPAS) to the Mayo Scheduling System (MSS). This caused delay in the implementation of PCS mailing letters along with the release form in the instances where the patient chose postal communication. During this delay, the MOS team mailed the letters manually. This was facilitated by the small number of patients and the uncommon use of postal communication (see below). Notwithstanding the delay, implementation of automated mail dispatch by PCS was accomplished in the second half of the trial period.

Anatomic pathology group

Figure-4 delineates steps involved in segment-2 of the process. Cytotechnologists use the outside report to select blocks most likely containing the best material (>60% tumor) for testing. If no block is identified as clearly having enough tumor per the report, all blocks with potential tumor are requested. With the introduction of COBAS® method, MolGen lab switched all testing to 5 µm thickness, resulting in standardized thickness of requested unstained slides (all 5 µm).

Cytotechnologists check if molecular testing was previously performed by evaluating the outside reports and by checking our institution's records for any prior molecular reports. If prior testing was performed successfully, the results are documented and linked to the patient's medical records, and blocks/unstained slides are not requested; only slides are requested to confirm the diagnosis. Once the material is requested, the medical secretary creates a patient packet and enters the patient information into the Slide Request Database and checks the pathology information system daily to verify receipt of material. If the material is not received within 2-3 business days, the secretary follows-up with the outside institution. Once the patient material is received, the case is flagged with "requested *BRAF/KIT* material" at the accessioning area and passed onto the MC3 area, where the

pathologist confirms the outside diagnosis and instructs the medical secretary to order the required molecular tests. If there were a disagreement with the original diagnosis, the case was to be shared with a second pathologist. However, no disagreements with the original diagnosis occurred.

A script and SOPs were also developed to guide AP staff on the procedure of outreach to outside institutions, handling and reviewing material for *BRAF/KIT* testing in melanoma patients. Finally, an educational PowerPoint presentation delineating the process and the responsibilities of each party was given and distributed to all AP team members. Data from this segment of the process was captured by the pathology informatics/project oversight group (table-1).

Molecular genetics / Molecular anatomic pathology group

Figure-5 delineates the steps involved in segment-3 of the process. Cytotechnologists, who are trained to identify tumor, review the slides and ensure that the selected block has sufficient (>1 cm) tumor for testing. If tumor is less than 1 cm, the decision whether or not to cancel testing is left to the molecular pathologist. If sufficient tumor is present, the selected material is sent to the histology lab for processing (if block is obtained). Once slides are returned to the cytotechnologist, molecular testing is performed according to SOPs (see methods) and the results are reported and incorporated into the medical record. The material is finally returned to the outside institution. Data from this segment of the process was captured from the molecular pathology report.

Pathology informatics / project oversight group

Table-1 delineates all the key checkpoints in the workflow process chosen for data collection. Over one year (June, 2012 – June, 2013), 55 patients (33 male and 22 female, mean age = 58.7 ± 14.9 years) went through the novel process. All patients were tested for *BRAF* and 12 had *KIT* testing. Twenty-eight patients (51%) had prior testing performed at an outside institution and 7 (13%) had been tested at our institution [a total of 35 (64%) had prior testing]. Detection of prior testing was made possible by the checkpoints created at the levels of MOS (by asking the patient during the phone call) and AP (by the cytotechnologist's checking the patient's outside molecular reports and our institution's records). The remaining 20 patients went through the new process; results were available before the patient's appointment in 12 patients and after the appointment in 8 patients. Overall, pre-appointment availability was 85.5% (47 of 55).

Segments 1, 2, and 3 of the process averaged 4.9 ± 3.7 days, 4.8 ± 1.4 days, and 3.8 ± 0.8 days. The overall process averaged 13.4 ± 4.7 days. The release form was communicated by email in 6 (30%) patients, by fax in 11 (55%) patients, and by postal service in 3 (15%) patients. In cases where results were incomplete at the time of the patient's appointment, results were made available at an average of 3.6 ± 3.2 days after the appointment.

Discussion

The emergence of personalized medicine is being driven by development of high-throughput technologies examining biological systems, such as Next-Generation Sequencing and

Whole-Genome Analysis [8, 9] and by the development of targeted therapies. Because treatment decisions are increasingly being made based on data generated from such technologies, management and timely delivery of this data is gaining importance. This task, however, is proving to be a challenge for the rising field of personalized medicine [13]. Among the data management challenges, creating robust workflow solutions for timely delivery of molecular data is pivotal.

We designed a process that allows for pre-appointment molecular testing to address this rising need and chose *BRAF/KIT* testing in advanced melanoma as a model. This choice was based on *BRAF* and *KIT* 's being an essential molecular test in the practice of oncology [14], the limited number of care providers involved, and the small number of patients. During the design and implementation of the new workflow, *BRAF* testing had become more routinely available in the community, explaining the relatively high percentage of patients who had molecular testing prior to making their appointments. During the trial period, 55 externally referred patients with metastatic melanoma had appointments; molecular results were available at the time of the appointment 85% of the time. The success was not limited to cases in which testing was completed prior to the appointment, as even in the instances (40%) where testing was complete after the appointment, the delay averaged 3.6 ± 3.2 days, a significant reduction in comparison to the original process. This allowed for earlier rendering of treatment plans, reduction of cost, increased patient satisfaction, increased efficiency of physicians, and an overall superior patient care. This success was made possible by collaboration of multiple divisions and commitment of their leadership. Since the process only alters the timing of testing and data collection (performed before rather than after the appointment), the process did not cause additional cost; the process was revenue neutral.

While it may have been attractive to optimize the approach to one disease (i.e. melanoma), it was important to examine the work from a larger perspective. It is anticipated that this approach will benefit other conditions. Therefore, we chose that the process developed be scalable. This proposed model in melanoma paves the road for similar processes in other conditions; several cancers in which the current clinical practice utilizes a battery of molecular tests can benefit from such solutions [15-20]. Furthermore, the scalability of the proposed workflow design in this relatively low-volume model sets the stage for later application in more complex and larger models, with the ultimate goal of creating a robust and complex system of molecular data management allowing for efficient and personalized targeted treatment plans.

The electronic health record was helpful in coordinating care in this process. However, a universal health record would be even more valuable, permitting rapid access to the laboratory reports. This, however, would not substantially speed up the process. On the other hand, universally accepted electronic signatures would permit use of web forms, which would speed up the process considerably. The study was also limited by the somewhat manual methods of data collection and monitoring, largely caused by lack of inter-compatibility between different information systems. More permanent and robust measurement methodologies built in the information systems should be used for ongoing process control. Moreover, replacement of single or small panel gene testing by more

complex methods such as Next-Generation Sequencing (NGS) will generate more complex multidimensional data streams requiring more elaborate data management solutions; computational challenges will involve each step including data handling, processing, annotation, data integration from different sources and platforms, and the clinical interpretation of the data [13, 21]. Our processes are independent of the testing method, i.e., NGS or limited panels, and will provide more efficient workflows, decreased turnaround time, and great patient and provider satisfaction. For the short term, limited NGS panels are providing more actionable results with less confounding data. Finally, certain demands created by incorporation of multiple large volume workflows in the process may create challenges for certain areas of the workflow. For instance, capturing and documenting data from multiple large volume workflows may create strain on the secretarial staff.

In summary, this study describes a scalable workflow solution that permits pre-appointment *BRAF/KIT* mutation analysis and rendition in melanoma patients, allowing molecular results necessary for treatment decisions to be available to the oncologist at the time of the patient's appointment. The successful implementation and scalability of this process sets the stage for further applications of this model of precision diagnostics in other conditions, answering an increasing demand for efficient delivery of molecular data in the era of individualized medicine.

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Figure 1.

Steps involved in the original process from the time of the patient's call to make an appointment to the time of making a treatment decision.

Cytotech: cytotechnologist, MAP: molecular anatomic pathology lab, MC3: Mayo Clinic 3, MICS: Mayo Integrated Clinical Systems, MolGen: molecular genetics lab, MOS: medical oncology scheduling, PCP: patient care provider, tech: technologist, WG: working group

Figure 2.

Key steps involved in the alternative process from the time of the patient's call to make an appointment to the time of making a treatment decision. More detailed steps of each segment are delineated in figures 3, 4, and 5.

Figure 3.

Steps involved in segment-1 of the process. It begins with the patient (or provider) calling to schedule an appointment with medical oncology at our institution after having been given a diagnosis by their primary care provider and ends with the patient being assigned a permanent medical record number (MRN).

MOS: medical oncology scheduling, MR: medical records, MRN: medical record number, PCP: patient care provider, PCS: patient correspondence, system,

Figure 4.

Steps involved in segment-2 of the process. It begins with the medical secretary in AP receiving the release form along with the cover letter from the appointment coordinator and ends with the receipt of the molecular testing material (slides) by the molecular lab cytotechnologist for pre-test review.

AP: anatomic pathology, cytotech: cytotechnologist, MC3: Mayo Clinic 3,

Figure 5.

Steps involved in segment-3 of the process. It begins with the molecular lab cytotechnologist reviewing the available patient slides and ends with incorporation of the molecular results into the patient's medical records and the patient's appointment with medical oncology.

Cytotech: cytotechnologist, MAP: molecular anatomic pathology lab, MICS: Mayo Integrated Clinical Systems, MolGen: molecular genetics lab, tech: technologist, WG: working group

Table 1
delineates all the key checkpoints in the workflow process chosen for data collection

Working group	Captured data
Medical oncology scheduling	<ul style="list-style-type: none"> • Patient call time • Patient appointment time • Prior <i>BRAF/KIT</i> testing • Form of communication of release form: • Email • Fax • Postal service • Time of receipt of completed release form from patient
Anatomic Pathology	<ul style="list-style-type: none"> • Time of receipt of completed release form/cover letter in anatomic pathology • Time of receipt of outside pathology reports • Number of institutions with available patient material (single vs. multiple) • Time at which outside material was requested • Time of receipt of outside material • Type of material received (blocks vs. unstained slides) • Time at which outside sides accessioned in our pathology computer system • Time at which confirmatory (MC3) pathology report is released • Agreement with outside diagnosis
Molecular genetics/Molecular anatomic pathology lab	<ul style="list-style-type: none"> • Time at which slides to be tested are reviewed by cytology technicians at the lab • Adequacy of slides reviewed by cytology technicians • Time at which the results of molecular testing (<i>BRAF</i> or <i>KIT</i>) are available in the electronic medical records