Implementation of Novel Precision Medicine Workflows in the Community Oncology Setting

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Introduction

The implementation of precision medicine in clinical oncology through next-generation sequencing (NGS) has provided oncologists and their patients ready access to extensive molecular information; in turn, oncologists can then offer their patients specific targeted therapies and improved access to clinical trials. Thus armed, both oncologists and patients are better able to make informed decisions.

In several cancer types, such as lung cancer, NGS has become standard of care (SOC), as several trials have established the superiority of certain targeted therapies over standard cytotoxic treatments with regards to toxicity and efficacy.[1] Moreover, several tissue-agnostic targeted therapies are approved by the US FDA that target a tumor's molecular driver regardless of the tissue of origin, suggesting that comprehensive molecular profiling through NGS might be appropriate for all tumor types. However, the rapid development of NGS technology and biomarker-based clinical trials has posed a sizeable challenge for medical oncologists attempting to stay up-to-date and offer patients

under their care the optimal course of treatment.

In an effort to realize the potential of NGS-based precision medicine, many cancer centers have instituted molecular tumor boards (MTBs) to support clinician decision making through the interpretation of NGS test results.[2] These MTBs are typically arranged at regular pre-scheduled intervals and are attended by a multidisciplinary team – oncologists, pathologists, geneticists, clinical trial coordinators, and other experts within an institution – that can translate a patient's NGS results into actionable changes to treatment plans or enrollments in clinical trials. Several studies have demonstrated that MTBs effectively guided treatment selection and improved clinical outcomes for patients.[1]

Though the utility of MTBs is readily apparent, there are significant practical challenges posed by a busy clinical practice that can reduce the optimal benefit of MTBs to affect point of care decision making. For example, while MTBs might occur at regular monthly intervals, the cadence of decision making in real practice is more frequent and sporadic. Similarly, the turnaround time between the receipt of genetic results and MTB output can be fairly significant and frustrating for clinicians and their patients. Data analyzed across several published reports indicate that the median time from the submission of a case to an MTB-supported recommendation ranges from 12-16 days, which in many cases would require weeks before a patient would be presented with options for a next course of treatments or potential clinical trial opportunities.[3,4]

Here, we present three alternatives to regularly scheduled MTBs to optimize the utilization of precision medicine into clinical practice. These point-of-care precision medicine support tools include: 1) the creation of an on-demand molecular helpline; 2) a process to identify currently eligible patients for new clinical trials; and 3) the use of practice-wide notifications about changes to biomarker-based changes to SOC (**Figure 1**). This multifaceted, near real-time approach to incorporating precision medicine into patient care not only serves as a powerful supplement to MTBs but also improves the speed at which insights from NGS data can translate into standard of care and clinical trial enrollment decisions.

Tennessee Oncology

Tennessee Oncology is one of the largest oncology practices in the country with over 200 oncology providers caring for patients spread over 30 sites of care throughout Tennessee and northern Georgia. Tennessee Oncology has a unique partnership with the Sarah Cannon Research Institute (SCRI) which provides access to cutting edge clinical trials and a precision medicine team. Through this partnership, Tennessee Oncology typically enrolls over 1,250 patients into clinic trials each year. Tennessee Oncology is part of the OneOncology platform that serves as a medical service organization. Clinical decision support tools to aid physicians in making the best decisions for patient care is a focus at OneOncology, which also maintains a database of somatic NGS testing results to aid physicians in its decision-making role.

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Precision Medicine Support Tools

1. On-Demand Molecular Helpline

Tennessee Oncology physicians have access to a consultation service embedded directly into their electronic medical record system (Flatiron OncoEMR). Upon receipt of a patient's NGS testing, a clinician can place a non-billable order through the EMR for a precision medicine specialist at SCRI to review and then interpret the patient's test results in the context of the specific patient's diagnosis and prior treatment. Within approximately 24 hours, clinicians receive near real-time feedback on standard of care mutation-specific therapies and available clinical trials across the network. Feedback is emailed to providers and also scanned into the patient medical record. For example, we piloted this at Tennessee Oncology and based on data from the first 120 patients reviewed, actionable mutations were identified in 103 patients with 27 subsequently enrolled in clinical trials. Average turn-around time from physician order to MTB feedback was less than 10 hours.[5] This near real-time tool not only fosters engagement by clinicians, but also allows clinicians to receive and relay clinical information to their patients in a timely manner, particularly during consultations regarding changes to treatment plans.

Feedback from the precision medicine specialists is comprised of functional characterization of variants (e.g., pathogenic, inactivating mutation in BRCA2), their therapeutic associations (associated with sensitivity to approved PARP inhibitors), and relevance to clinical trials (being investigated for new DNA damage repair agents as a part of a clinical trial). An important differentiator to other clinical trial recommendation tools is that the matching is performed at the level of the individual cohort or arm of the clinical trial and, furthermore, the precision medicine specialists work together with the enrollment teams to monitor slot availability. These result in truly actionable clinical trial recommendations based

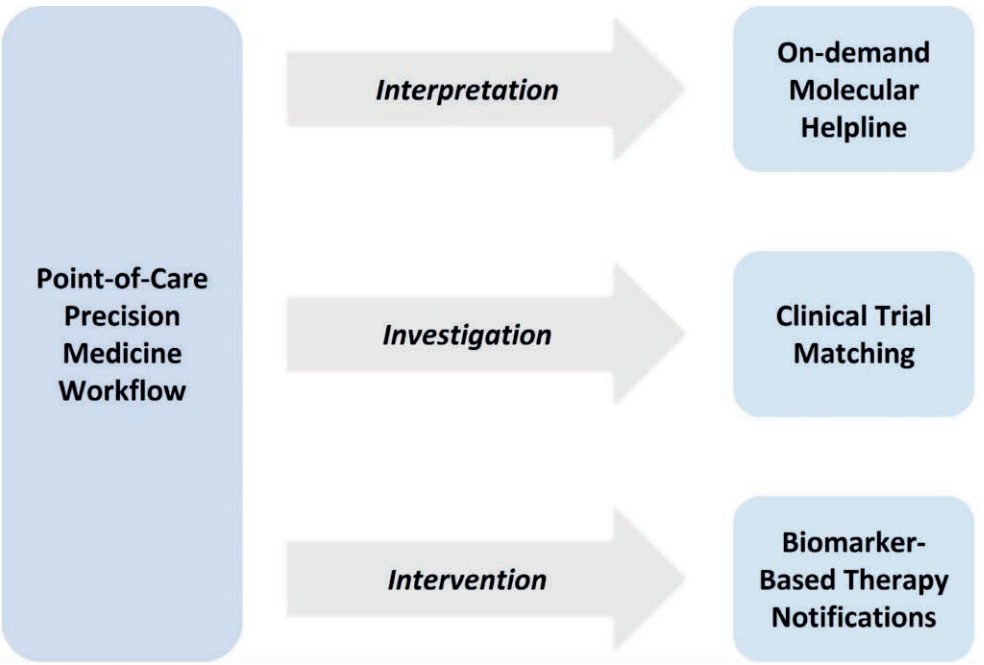

Figure 1: Near Real-time Precision Medicine Workflow Complement to MTB

on the molecular results of a patient's tumor and are not hypothetical matches based solely on information provided in publicly-available clinical trial resources (e.g., www.clinicaltrials.gov).

2. Clinical Trial Matching

The complexity of clinical trials has increased and requires more sophistication to understand study designs, track amendments and cohort openings/closing, and interpret biomarker criteria. These complexities, in part, lead to the overall poor participation in oncology clinical trials. To reduce barriers to access, Tennessee Oncology has worked to perform real-time clinical trial matching for patients with mutation-driven tumors. For clinical trials that require a biomarker status (e.g., FGFR3 fusions), a machine-readable rule is generated and NGS data across the Tennessee Oncology practice locations is queried to identify all currently active patients with the appropriate NGS result.

For the purposes of clinical trial matching, "active" patients are defined as patients with an NGS result who have had an appointment in the previous two weeks or have one scheduled in the next two months. Lists of appropriately-matched patients are then emailed to principal investigators (PIs) and treating physicians to make them aware of clinical trial opportunities and coordinate referrals to clinical trial offices. These lists of matched patients are provided on a regularly-occurring basis and provide valuable information to treating oncologists, study PIs, and pharma sponsors. Importantly, as the studies progress and new/different cohorts open or previous cohorts close, the rules are modified to only match patients to the currently-available portions of clinical trials.

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3. Biomarker-Based Notifications

As the oncology clinical research field advances, so does the prevalence of approved precision oncology agents available in the standard of care space. While NGS testing is being incorporated into standard clinical practice, there remains a gap in making sure that all patients with NGS results get access to newly-approved precision oncology agents. To close this gap, Tennessee Oncology takes advantage of biomarker-based notifications that are sent to treating physicians when a new precision-oncology agent that requires a biomarker status is approved. These notifications include the new agent's FDA label, a brief summary of the mechanism of action and biology, and a list of patients with appropriate molecular results that would qualify them to get access to the newly-approved agent. For example, following the FDA approval for sotorasib in KRAS G12C mutated non-small cell lung cancer, we were able to find every living patient who met criteria for its use and notify their providers of the new approval.

What makes these notifications critical is that in numerous cases biomarker testing may have been performed several months or even years prior to the approval of the new agent; coordinating new approvals with previous molecular testing results *at scale* remains a challenge. Introducing biomarker-based notifications reduces the burden on the general medical oncologist, ensures that all patients with appropriate biomarker testing results are flagged for potential targeted therapies, and centralizes these processes for metrics gathering and reporting.

Conclusions

With the increasing number of biomarker-based FDA drug approvals and testing incorporated into early- and late-stage clinical trials, this progressive paradigm has been shifted towards the implementation of NGS results into routine clinical care. This growing movement has laid bare the importance of ensuring that the traditional roadblocks posed by the interpretation of NGS data is alleviated.[2,6]

Adding to this momentum is the growing realization that the current practice of relying on regularly scheduled MTBs to interpret and disseminate valuable patient genomic information to busy clinicians, while a vital part of a multidisciplinary approach to care, is often the rate-limiting step in determining a patient's optimal treatment. As such, the current standard practice may actually reduce physician engagement and limit the effectiveness of physician-patient engagement. Given that our processes utilize electronic communication to provide timely responses, there is limited opportunity within the workflow for the interactive multidisciplinary communications integral to MTBs. As such it is important that both these approaches are not treated as mutually exclusive options, but rather complementary services that enable optimal patient care.

The on-demand, cross-functional processes described above enable rapid and comprehensive interpretation of NGS reports, identify patients eligible for new clinical trials, and identify patients harboring mutations that have new targeted therapies approved and can reduce delays in care, improve physician engagement, and ensure precision medicine is optimally integrated into routine practice. JoPM

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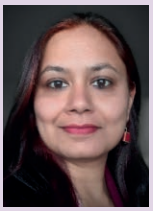
Davey Daniel

Dr. Daniel serves as the Chief Medical Officer of OneOncology. Dr. Daniel is currently the Vice Chair of OneCouncil, the platform's all-physician advisory board for clinical and strategic initiatives. He leads medical education initiatives, including virtual tumor boards, a physicians' conference that OneOncology will hold in the fall of 2022 and other learning opportunities for physicians and fellows. Daniel has also been integral to launching OneCommunity, a digital oncology platform used to examine medical cases at practices across the partnership.A lung cancer specialist who treats patients at Tennessee Oncology in Chattanooga, Dr. Daniel received his medical degree from Johns Hopkins School of Medicine and did his Fellowship at Duke University Medical Center.

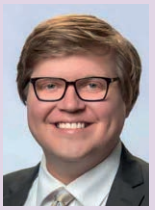


Neha Jain

Neha Jain serves as the Senior Director of Precision Medicine at OneOncology. She has had almost a decade of precision medicine experience in which she has built and scaled molecular tumor board to oncologists. Her focus has included the launch of a virtual international tumor board (Our Cancer Genomes) and numerous initiatives to improve trial enrollment through molecular services.

Hari Raman

Hari is currently serving as a clinical intern at OneOncology, and has prior experience with IMS Consulting Group as a management consultant in the biopharmaceutical space. He earned a Bachelors of Science from Columbia University and received his MD at Washington University in St. Louis and is currently serving as a resident physician at Brigham and Women's Hospital/Harvard Medical School training in Internal Medicine. He is also concurrently pursuing an MBA at Harvard Business School.



Andrew McKenzie

Dr. McKenzie joined Sarah Cannon in 2015 and serves as the vice president of Sarah Cannon's Personalized Medicine Program. He also serves as the scientific director for Genospace, Sarah Cannon's precision medicine platform. In his role, Dr. McKenzie is responsible for providing scientific and operational oversight for implementing Sarah Cannon's personalized medicine strategy. He and the personalized medicine program provide scientific, consultative and programmatic services to clinical research investigators, study sponsors, research personnel and other healthcare providers to advance Sarah Cannon's molecular profiling efforts. Prior to joining Sarah Cannon, Dr. McKenzie was a research fellow in the cancer biology department at Vanderbilt University's Vanderbilt-Ingram Cancer Center where he investigated extracellular vesicle trafficking and translational cell biology research. He earned a Bachelor of Science from Shorter College and a Doctor of Philosophy in pharmacology from The University of Vermont where he investigated extracellular matrix remodeling and cell motility.

Duncan Allen

Duncan Allen joined OneOncology in 2019 where he currently serves as Senior Vice President of Clinical Services. As a leader in oncology, he has helped develop the clinical platform for one of the fastest growing oncology groups in the country with more than 850 providers caring for ~.5M patients annually across 200+ sites of care nationally. Allen has overseen the deployment of many new services including the OneOncology research organization ("OneR"), launch of concierge precision medicine services, development of a clinical support technology designed for oncologists, the founding of OneCouncil the clinical advisory board of OneOncology and more recently has been focused on leading the Enhancing Oncology Model efforts for OneOncology. Allen spent six years at Vanderbilt University Medical Center, where he served as Administrative Officer, Vanderbilt-Ingram Cancer Center with responsibility for multiple service lines. While at Vanderbilt Allen focused on the development of multiple novel clinical programs in cellular therapy and radioligand therapy. Allen received his BA and Masters of Healthcare Administration from the University of North Carolina at Chapel Hill.

Thomas Stricker

Thomas Stricker joined OneOncology in 2022 as the Medical Director for Precision Medicine. Dr. Stricker was most recently an Assistant Professor in the Department of Pathology, Microbiology, and Immunology at Vanderbilt University where he founded the Somatic Clinical Sign-out Team and the Clinical Genomics Lab, which generates whole exome and other germline sequencing panels. Dr. Stricker also served as associate director of VANTAGE, the research sequencing core for Vanderbilt. Dr. Stricker earned his MD and PhD from Washington University in St. Louis, followed by a residency in Anatomical Pathology and a fellowship in Bone and Soft Tissue at The University of Chicago.

Stephen Schleicher

Stephen Schleicher, MD, MBA, was appointed Chief Medical Officer (CMO) of Tennessee Oncology, one of the largest providers of oncology care, in January 2022. In that role, Dr. Schleicher oversees clinical programs to promote the high-quality, innovative and patient-centered care Tennessee Oncology is known for delivering throughout Tennessee and North Georgia. Dr. Schleicher, who joined Tennessee Oncology four years ago, has served as Medical Director of Value-Based Care across both Tennessee Oncology and OneOncology, a national platform for independent community oncology practices that now includes over 850 providers caring for ~.5M patients annually across 200+ sites of care nationally.. Dr. Schleicher received his medical training from Harvard's Brigham and Women's Hospital and Memorial Sloan Kettering (MSK) in New York before returning to his hometown of Nashville to join Tennessee Oncology. Dr. Schleicher also spent time as a consultant at McKinsey and Company before completing oncology fellowship training at MSK where he focused on understanding the intersection of Accountable Care Organizations and Cancer Care. In addition to his role as CMO for Tennessee Oncology, Dr. Schleicher serves as President of the Tennessee Oncology Practice Society.