Clinical data and precision medicine:

The urgent need for in-house NGS capabilities at community hospitals

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Creating Actionable Genomic Results to Inform Precision Medicine at Community Health Centers

We are now at a point where genomic insights and pharmaceutical research are in confluence, allowing a patient's genetic code to be directly linked with a targeted therapy. Yet difficulties remain for the majority of cancer patients to access these new treatments in a timely fashion, as many hospitals do not offer genomic testing that might match a patient with a targeted therapy on site. Even if patients have access to comprehensive molecular profiling through outsourced testing, that process can take a long time to provide results and insights – in some cases up to two months. This often-lengthy turnaround time for testing ultimately affects the ability of doctors to use the results to treat patients, particularly when an expeditious intervention may be critical for late-stage cancer patients.

We, as healthcare providers, take the stance that comprehensive genomic profiling needs to be a standard of care for the treatment of cancer. So, what can we do to ensure that every cancer patient has access to this testing and information in order to receive optimal care? And how can we secure this access for smaller community hospitals that may not have the same resources or internal expertise as larger academic medical centers?

We recently addressed these two questions at William Osler Health System (a community health system based just outside Toronto, part of a publicly funded healthcare region). As a result of our investigations, we were able to bring comprehensive next-generation sequencing (NGS) in-house at our facility. Bringing NGS in-house has ultimately allowed us to introduce precision medicine within our oncology department so we can deliver more informed and efficient patient care and achieve better patient outcomes.

Urgent Focus for Community Hospitals

Academic medical centers are thought of as the most cutting-edge destinations for patient care, often due to their unparalleled access to new technology. Most patients, however, are not treated in academic medical centers, but instead receive care at their community-based health system that are not equipped with the latest testing or treatment capabilities. Equitable delivery of the same quality of care for patients, whether at academic- or community-based medical centers, is essential for community health. While waiting for NGS data from outsourced partners, patients are often started on a traditional therapy (e.g., radiation or chemotherapy), which may not only be less effective but also come with harsh side effects. When the results finally come back and indicate that the patient may be a match for a targeted therapy, they may need to wait until their body recovers from initial treatment to begin a new treatment regimen. Not only are patients put at risk by the delay, but the health care system is also charged with needless costs.

These scenarios will be more common as the number of precision medicines available for cancer continues to grow. We need to be sure patients treated at community health centers can be matched to these targeted therapies *before* they are

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placed on another treatment plan. Insourcing NGS is one solution to ensuring comprehensive genomic results are available when making care decisions.

NGS uses similar principles to Sanger sequencing at a high throughput or massively parallel level. Traditional setups of these techniques relied upon a lengthy workflow including extraction of nucleic acids, library preparation, and bioinformatic analysis. This high-content technology has been out of reach for community hospitals due to financial restrictions and a lack of trained technical staff to operate the equipment. Additionally, most physicians were not trained to use NGS during their residency programs. It is a new skill that needs to be learned, and there is still an educational gap on the professional side.

In the last five years, novel NGS technology has become available that condenses the entire workflow into a single instrument that can be operated by a single user. While the core technology is unchanged, this streamlined delivery has brought NGS within grasp for community-based practices like Osler. Introducing NGS assays directly into community-based practices is helping bring testing closer to the patient earlier in their care journey.

Osler's Journey to Integrate Precision Medicine

When we set out to start a molecular oncology program in 2017, patients had access to single-gene testing via outsourced testing. Every single cancer-related test was being referred out to a nearby academic center, and it took, on average, two months to return the results to patients. We quickly realized if we wanted to see real patient treatment impact from this testing, we needed to speed up turnaround times. The most economical way for us to get started was through bringing select single-gene testing in-house.

We had already been working on immunohistochemistry (IHC) testing in our anatomic pathology lab to identify markers like HER2 protein overexpression in breast cancer. Like other community hospitals, we handled these tests very well and were able to quickly turn results back to the provider for these biomarkers. When we expanded to add single-gene molecular testing, instead of setting it up in a separate molecular lab, we brought it into the same area, under the same management as IHC, so we have results from both modalities available together – in a single day.

With insourced single-gene testing, we established a median turnaround time for lung cancer biomarkers of four days. In turn, 94% of patients had complete biomarker information available at their first consult with an oncologist, compared to just 17% when we were outsourcing testing to a reference lab. (**Figure 1**)

As even more targeted therapies became available for additional cancers, we quickly realized we were running multiple single-gene tests to match patients with the right targeted therapy. Looking at the full picture of cost and resources, we ultimately decided to bring comprehensive genomic sequencing in-house, which has allowed us to essentially run more than 50 single-gene tests combined in a single assay. This approach offers a more complete picture to match patients with the optimal treatment.

Evaluating the Options

When we first decided to bring NGS in house, we partnered with Thermo Fisher Scientific to find a solution that would work for our lab. Given our limited resources, the fully automated Ion Torrent Genexus System was the best fit, as it integrates several elements of the NGS workflow including library preparation and bioinformatic analysis. This simplified setup allows for the instrument to be operated by a histotechnologist with minimal training in molecular methodologies.

We recently validated the Genexus System and the Oncomine Precision Assay, a pan-cancer assay for the most prevalent cancer-driver variants, for clinical use. When placed within the anatomic pathology lab, and operated by histotechnologists, this ultimately unlocks the ability to integrate morphology, IHC, and NGS data into a single report. This workflow has been able to identify biomarkers in a comprehensive report, resulting in a sharp decline in the number of biomarkers reported as an addendum because all relevant biomarkers are captured in the comprehensive genomic sequencing data.

The turnaround time is so short that biomarkers can now be included in the diagnostic pathology report. This means it is easier for oncologists to get the information that's needed, and communication between the lab and clinic is more clear and succinct. Additionally, NGS data can now be used by pathologists to augment their diagnostic abilities.

The Patient Experience

Cancer patients typically receive their initial diagnosis from a family doctor, radiologist or surgeon. They then must spend several anxiety-filled weeks waiting for their oncology consult wondering what's going to happen to them and what their treatment is going to be. As noted above, the patient may even be started on a substandard chemotherapy while they wait to see if they are eligible for a more targeted therapy (depending on the wait time for test results and the cancer progression).

In many community settings, oncologists submit the request for NGS after the patient's first oncology consult and schedule a follow-up to review the results and treatment options. Now at Osler, with NGS available in our own lab, most of our cancer patients have comprehensive molecular profiling results available when they first meet their oncologist. This seemingly simple shift has transformed cancer care for our patients.

Insourcing NGS not only saves precious time and anxious waiting for patients, but also reduces wasteful and unnecessary healthcare treatments. In our current workflow, when a patient shows up for their first oncology appointment after receiving a diagnosis, their NGS results will be there waiting for them. They will know at that first visit what

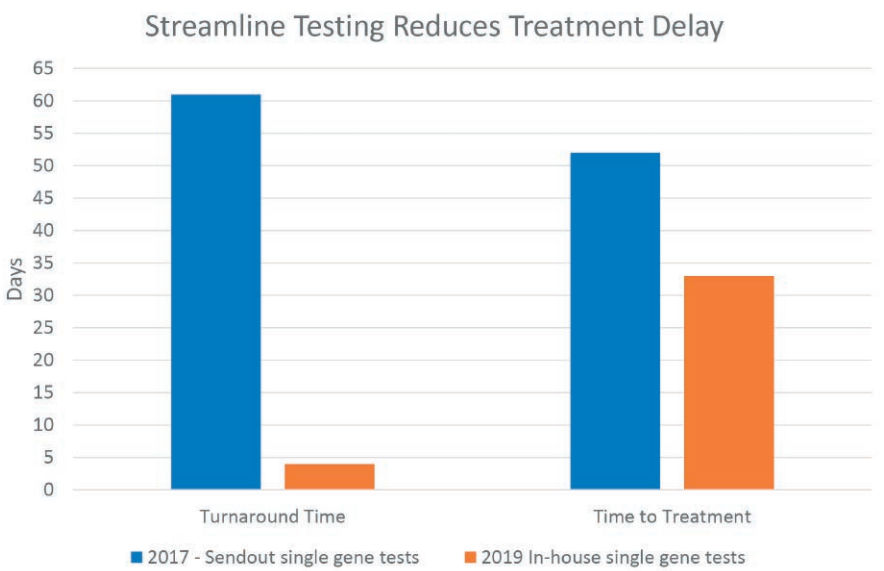


Figure 1: Comparison of turnaround time for test results and time to treatment for patients using outsourced single-gene testing (2017) and in-house single gene tests (2019)

their treatment is going to be – and that it's going to be the best possible treatment based on their genomic indications.

Areas of Immediate Improvement: Lung Cancer Treatment

After insourcing NGS, we saw one of the most immediate improvements in patient outcomes and cost savings in lung cancer. In Canada, lung cancer is the leading cause of cancer-related death. Modern treatment of lung cancer is simply not possible without biomarker data.

While running single-gene tests ourselves allowed us to access test results much faster, we found that for some cancers, like lung cancer, we were running upwards of seven different single-gene tests and still left with an incomplete picture. Switching to comprehensive NGS markedly expanded the number of actionable markers for which we are testing.

"When we did a cost comparison at Osler, we found that bringing NGS in-house and looking at all cancer-driving genes with just one test was the more economical option than continuing to rely on single-gene testing. The additional savings on shipping, accessioning, and stenography further bolstered the cost savings."

MET exon 14 skipping alterations are a prime example. There is no good single-gene test for these events, so they were not being routinely tested, despite the fact that well-tolerated oral therapy is available for patients with this mutation. Since commencing NGS testing, we have identified a large number of these events, enabling improved outcomes and quality of life for these patients with highly-effective pill-based therapies.

Securing Organizational Buy-In for Precision Medicine

Health system administrators may champion precision medicine as a concept, but when it comes to execution it can be more challenging to garner necessary support. As a case in point, community-based NGS is still relatively new, so it is essential to show the impact NGS will have on various departments to secure buy-in across an organization. Therefore, to succeed in bringing NGS capabilities in-house, hospital administrators need to form a team that includes oncology, surgery, and other clinicians such as radiologists, respirologists or gastroenterologists (depending on the specific scenario) to demonstrate the staff commitment to back the investment. At Osler, having the backing of a multi-disciplinary team helped us secure support from internal stakeholders.

Making the Business Case

When we were first trying to sell the concept of bringing NGS in house, we also recognized that we needed to build a business case. Financial barriers to precision medicine are among the most difficult to overcome, particularly in a publicly-funded healthcare system. Despite the immense promise and clinical benefit, the perceived fiscal hurdle of bringing NGS in-house can seem insurmountable. In community hospitals with tight margins, the business case can be just as important as the clinical case. We're hoping that what we have built at Osler can serve as a model other community practices can follow.

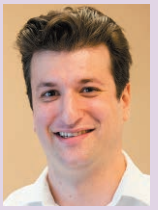
While the cost of NGS has been slowly falling over the past two decades, investing in in-house NGS still represents a new and, until shown otherwise, an unjustifiable cost for many health centers. This can make it harder for facilities with narrower margins to find the budget to invest in the equipment needed. When we did a cost comparison at Osler, we found that bringing NGS in-house and looking at all cancer-driving genes with just one test was the more economical option than continuing to rely on single-gene testing. The additional savings on shipping, accessioning, and stenography further bolstered the cost savings.

The true cost of delivering NGS data for clinical care is poorly understood. One thing we do know is that the most expensive component is the people – the technologists, not the pathologists. Using a fully automated process, we were able to train one of our existing histotechnologists to operate our system, eliminating a major cost while simultaneously benefitting from their acumen with scanty specimens. In addition, having comprehensive results available at first consult has provided a dramatic cost savings by eliminating the need for most patients to book a second oncologist consult just to review test results.

This is particularly important given that survival benefits stemming from improvements in disease detection and treatment have the potential to manifest in profound benefits to public health. When considering the cost-benefit analysis from the patient perspective, this allows our patients to be started on the appropriate therapy earlier in their care journey when results are first available. In many cases, this means a shorter recovery time, quicker time to remission, or simply a less invasive therapy option – allowing them to feel more like themselves without the harsh side effects that often come with first-line therapies like chemo and radiation.

Bringing Precision Medicine to All Patients

As clinicians, we have the opportunity and responsibility to bring the benefits of precision medicine to more patients. We can catalyze this advance first, by bridging the disconnect between where the majority of cancer patients are treated and where the best cancer treatments can be found and second by leading the adoption of comprehensive molecular profiling in our own facilities and communities. We can ensure that all patients have access to the most beneficial treatments and are provided the best care possible. With new advances in NGS that make gene-based data more accessible for community-based health centers, it is now up to clinical teams to advocate for and adopt NGS for patient benefit. JPM



Brandon Sheffield, MD, FRCPC

Dr. Sheffield is an anatomic and molecular pathologist. He is currently serving as the Division Head of Advanced Diagnostics and the Physician Lead of Research for the William Osler Health System in Canada. Dr. Sheffield focuses on the delivery of personalized medicine and precision oncology and making molecular testing available to community cancer patients in Canada.

Aimée Langan, MHSc, MSc

Director of laboratory medicine and diagnostic imaging. Aimée Langan has nearly two decades of experience in health administration, including experience within Canada's largest academic centres, and Cancer Care Ontario, one of the largest publicly-funded cancer care agencies in the world. Aimée's interests include the delivery of state-of-the-art cancer care with an eye towards fiscal responsibility that is necessary when working in a publicly funded system.

Andrea Beharry, MLT

Charge Technologist of Advanced Diagnostics. Andrea Beharry is a medical laboratory technologist, and helped build the immunohistochemistry program at the William Osler Health System. She has implemented testing to support breast cancer treatment, immuno-oncology, and others. After perceiving the immense unmet need, Andrea has learned to perform next-generation sequencing and other molecular assays. Combining these modalities has enabled her lab to deliver some of the most comprehensive biomarker reports available.