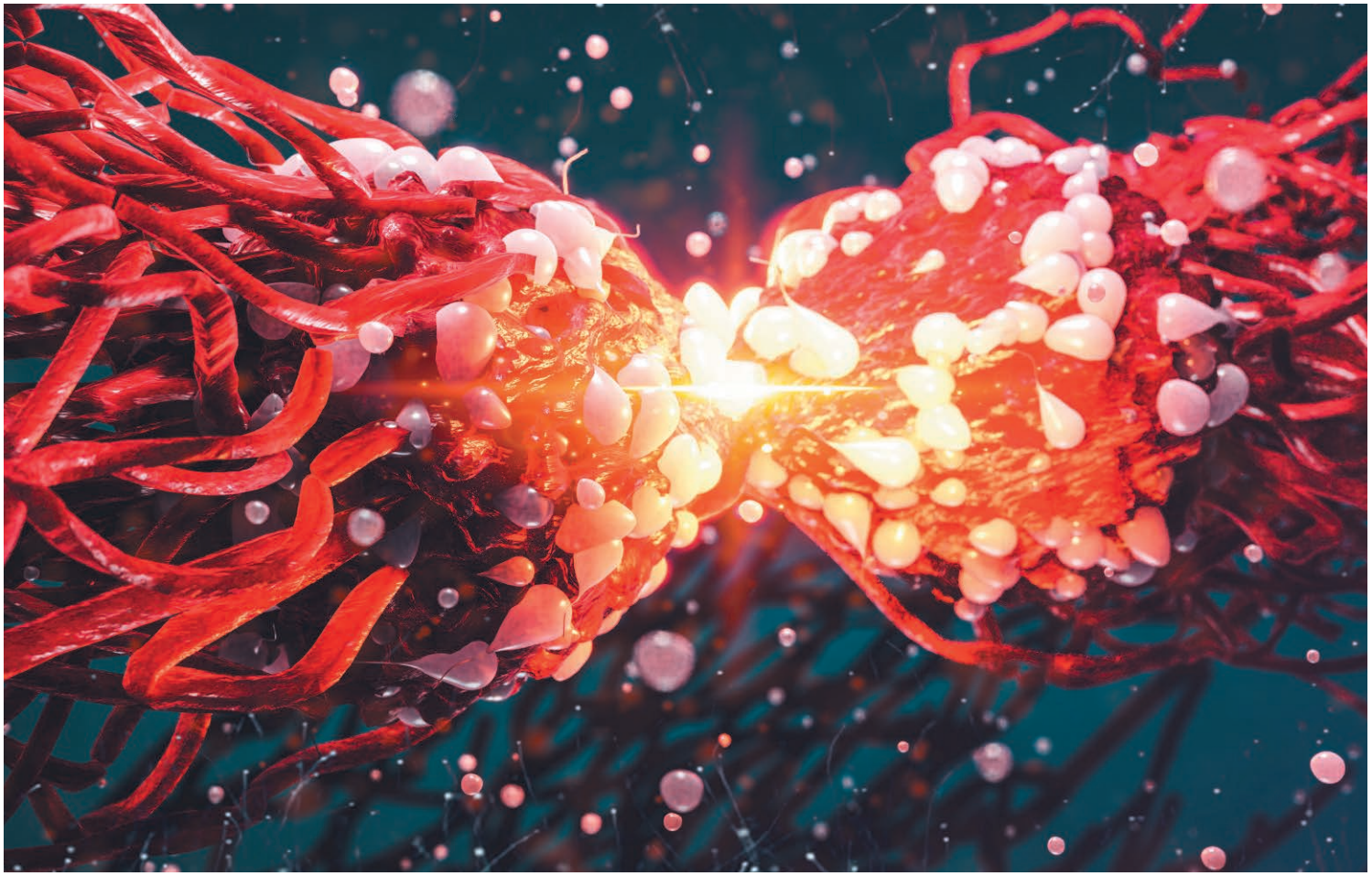

Part 1:

Industry challenges and opportunities for the integration of precision medicine tools at the point of care

By **Leah A. Nida, Evelyn Siu, Dan Van Tran and James Hamrick**

Introduction

Patient treatment in oncology is increasingly shifting towards personalized care by healthcare professionals using precision therapeutics and diagnostics. In the past five years, the healthcare industry has started to see alignment across the entire healthcare ecosystem – the payer, patient, physician, and pharma – that each patient's care should be individualized based on their unique cancer genetic and related clinical biomarker profile. Scientifically, the number of biomarker-driven therapies is growing. In 2019, over one-third of all oncology clinical trials were biomarker-driven.[1] The healthcare technology supporting clinicians in delivering precision medicine, however, still leaves much to be desired. In this paper, we outline the challenges and opportunities that the healthcare industry faces for the integration of precision medicine tools at the point of care. We discuss systems and solutions to this challenge in a follow-on paper.

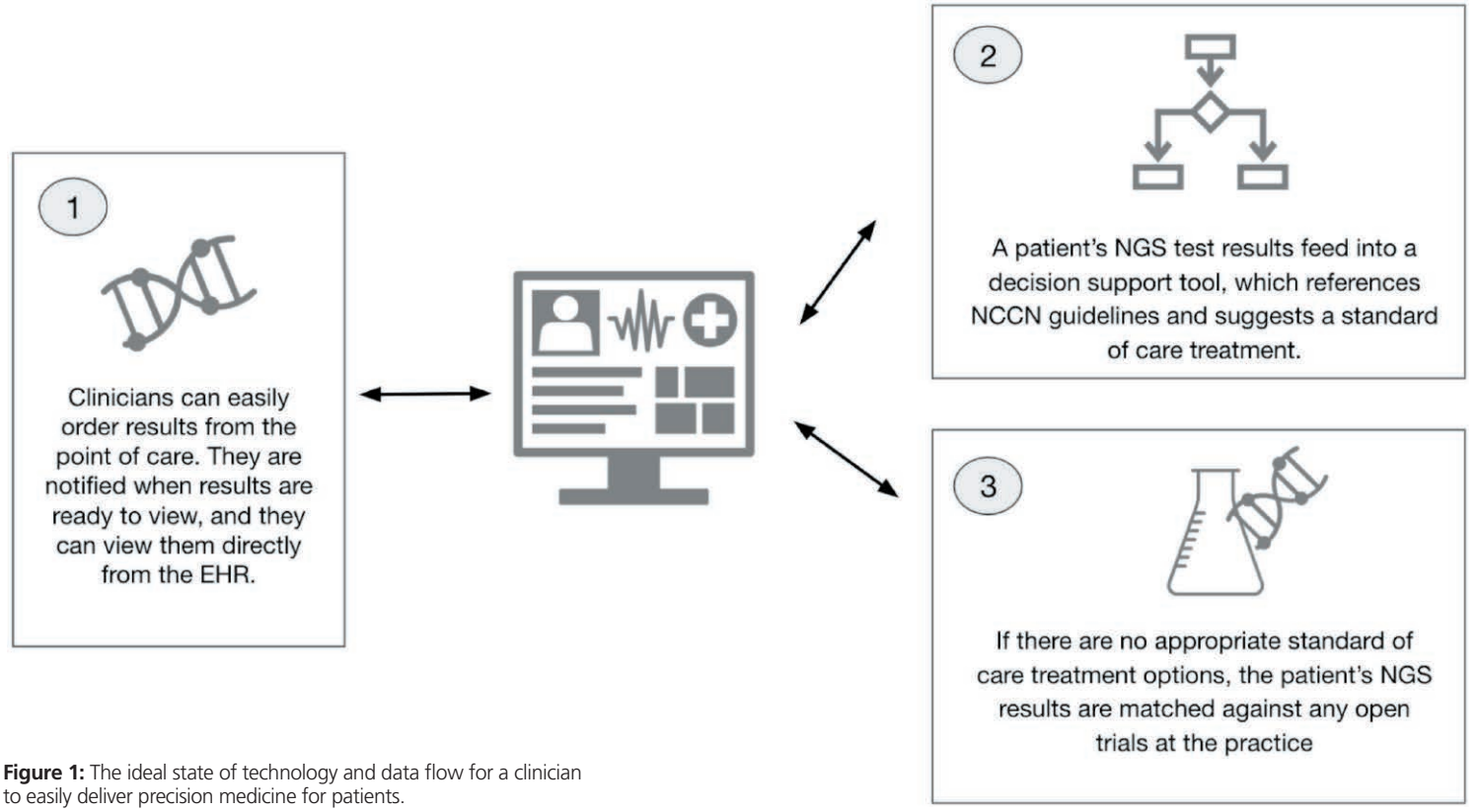

Figure 1: The ideal state of technology and data flow for a clinician to easily deliver precision medicine for patients.

Needs and Requirements

A clinician delivering personalized healthcare will need several pieces of information before making a precision treatment decision. They will need to know, among other details:

- the patient's cancer genetics, obtained through a genomic testing vendor,
- treatment therapies available based on the patient's genomic testing results,
- relevant NCCN guidelines, and
- the clinical trials that are available to that patient.

Much of this information is changing at a pace faster than clinicians can track, let alone digest. New treatments are approved, new clinical trials are opened at their practice, and new genetic variants are discovered and released for clinical tests. Not only do clinicians now have the burden of trying to keep up with a body of knowledge that is advancing quickly under their feet, but they also need to continue to treat their patients and run their clinics. Hence, clinicians need assistance keeping up with all of this information while they continue to treat patients. Timing is also critical. Clinicians must have the appropriate information available before they decide on a treatment plan for the patient. The goal is to get the right information surfaced to the clinician at the right time in the right place in order to test the patient and then get the patient on the right therapy or clinical trial.

"If there are no appropriate standard of care treatment options, the tool cross-references the patient's NGS results with any open clinical trials at the practice and suggests trials where the patient matches key trial eligibility criteria."

The Ideal State

Ideally, all of this information is available to clinicians through the electronic health record (EHR), their central source of truth for patient information (**Figure 1**). Imagine a world where clinicians can easily order results and be notified when the results of a patient's NGS test from the EHR are ready to view. The patient's NGS tests are automatically input into a decision support tool that parses the test results and cross-references the results with NCCN guidelines to suggest a standard of care treatment. If there are no appropriate standard of care treatment options, the tool cross-references the patient's NGS results with any open clinical trials at the practice and suggests trials where the patient matches key trial eligibility criteria. This information is provided to the physician directly at the point of care before they see the patient, so they can make an informed treatment decision.

Unfortunately, even though we have the technological capabilities to accomplish this today, this reality does not yet exist. This reality first requires easy and standardized ingestion of data in a structured format. Numerous industry challenges must be sorted out before this ideal state is possible. The main challenges the industry faces today are: a lack of interoperability standards, different specifications for testing and/or different machines used, and a variation in what is included in genomic testing results. Additionally, significant barriers remain with regards to the analytic capabilities of NGS and the current state of genotype/phenotype knowledge. Each of these three challenges will be addressed in the following sections.

1. Lack of Interoperability Standards

The ideal state requires EHR vendors to easily upload and parse information from NGS testing vendors, NCCN guidelines, and clinical trials databases. This requires all vendor platforms involved to offer structured data in an interoperable format. To realize the potential of true interoperability, standards for data representation and annotation, content requirements, and transport specifications must be reviewed

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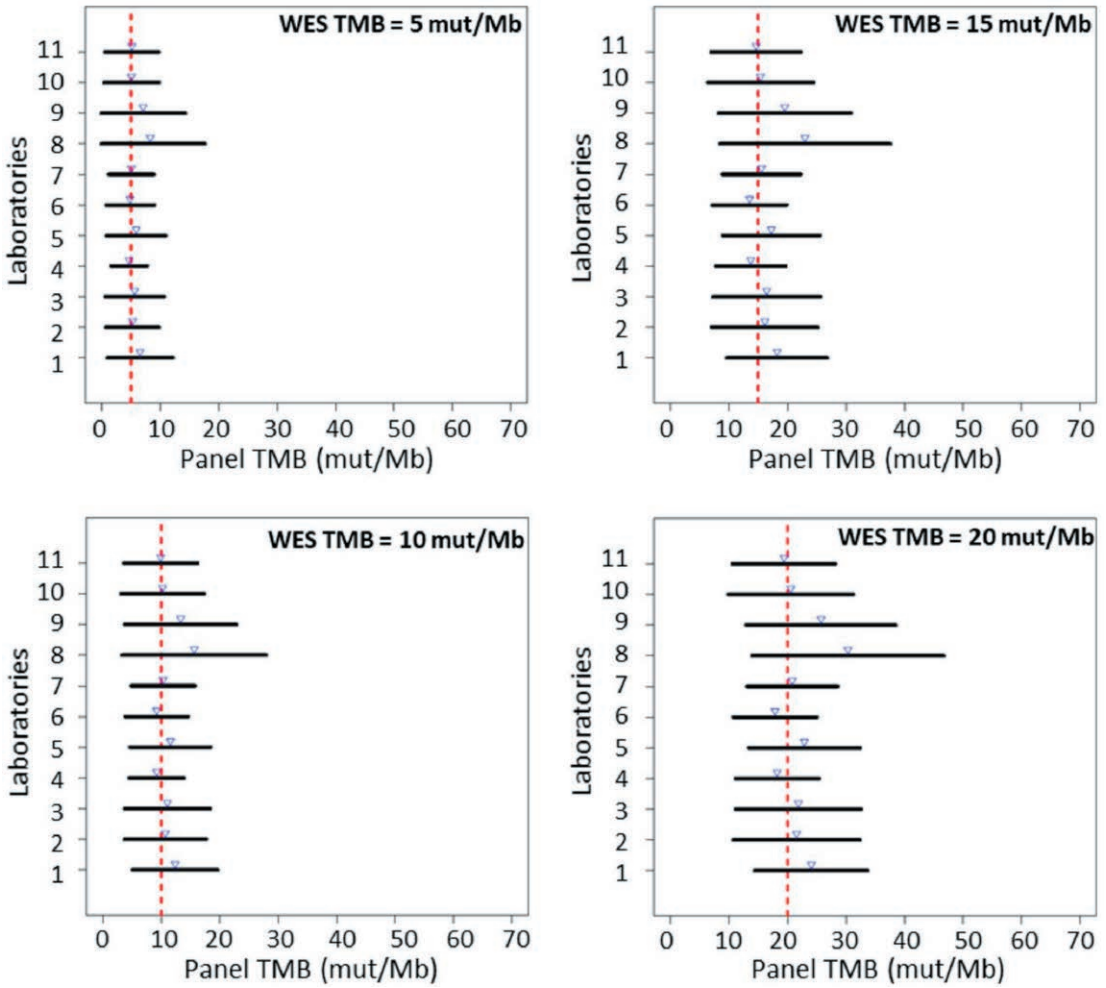

Figure 2: Graph shown in Merino *et al.*[4] that demonstrates variation in TMB quantification across different (anonymized) laboratory's diagnostic platforms, as denoted by the blue arrows. The red dotted line indicates TMB quantification by whole exome sequencing (WES), which is the most accurate quantification of TMB.

iteratively and then widely adopted once all parties are harmonized on the standards. Older transport standards such as HL7v2,[2] which is currently the standard by which to transport patient laboratory results, are not ideal mechanisms for transporting the rich genomic information produced by NGS testing. The informatics industry is currently creating such standards to increase the ease of data sharing amongst different platforms, utilizing FHIR and more specifically, MCODE.[3]

Today, with the lack of interoperability, systems at testing labs cannot easily communicate with the EHR. Patient genomic results are typically transmitted as a PDF document, a form of unstructured data. While clinicians are accustomed to obtaining the information needed to make decisions about their patient's treatment utilizing these PDFs, the EHR is unable to ingest the data from the PDF to use in other places. This causes the clinician to either have to enter the genomic information manually into a clinical decision support module or other area of the EHR, or to put the information in their visit note. As the industry moves toward interoperability between systems, discrete structured data elements as well as the PDF document will be easily transferred between systems, allowing EHRs and other systems to easily ingest, store, and utilize genomic data to surface the correct information, at the correct time. Having this level of interoperability will also allow healthcare technology to progress from simply displaying the data elements, to applying deep analytics that accelerate insights and outcomes.

"In addition to interoperable systems, genomic testing results are not currently standardized across NGS testing vendors and thus need to be harmonized within the receiving systems."

2. Different specifications for testing and/or different machines

In addition to interoperable systems, genomic testing results are not currently standardized across NGS testing vendors and thus need to be harmonized within the receiving systems. Today, many vendors have different specifications for testing, or use different machines. As a result, the outputs listed in a NGS report must be additionally interpreted based on that vendor's custom specifications.

One example is tumor mutational burden (TMB, see **Figure 2**). TMB is a value from a genomic testing panel that helps to indicate how likely a patient is to respond to an immune checkpoint inhibitor. TMB is most accurate in a whole exome sequencing panel, but NGS testing provides TMB value estimates in a much more cost-effective and timely manner. As shown in the figure, differences in panel size and gene coverage, as well as differences in underlying bioinformatics

pipelines, lead to variations in the TMB estimate presented to the clinician in the NGS testing report.

Therefore, the TMB value may indicate a different treatment path depending on which vendor conducted the NGS test. The TMB measurement alone, if simply reported as a number without accompanying context such as testing lab, method, and sample size, etc. may not be enough to make informed decisions. Until recently, different papers regarding the same disease would use different classifications of TMB High / Low. A patient with TMB = 10 mut/MB might be considered as TMB high in one paper but as TMB low in another paper. There are also different definitions of what TMB high means across diseases. Diseases like melanoma that are known to have high mutation rates will often have a higher TMB value than diseases like prostate cancer, etc. Clearly, lack of specification and interoperability can lead to ambiguity for the clinician at the critical stage of assessing a patient's status. Work is currently underway to build harmonization standards for TMB values.

3. Variation in terms of what is included in the report.

Above, we spoke about the difficulty of harmonizing genomic test results, however, we see the same harmonization difficulties in the expression of the biomarker and other data needed to help guide treatment decisions. For example, HER2 can be represented in many forms: ERBB2, human epidermal growth factor receptor 2, NEU, HER2, etc. Testing vendors may use any of these representations in the transmission of structured genomic testing results. This then requires the receiving EHR to harmonize and represent these variations in the most clinician friendly way.

This difference in representation not only causes additional work by the receiving system to display the genomic results but can make it difficult to ensure all of the actionable genomic data can be seamlessly used in other areas of the EHR. As the EHR works to reduce clinician burden by presenting the right information at the right time, this barrier becomes more burdensome.

Significant barriers relate to analytic capabilities of NGS and our state of genotype/phenotype knowledge

NGS testing is becoming more actionable, faster, less expensive, and more widely adopted. Information included in genomic test results is often hard to apply to the patient, as the consequences of many variants are yet unknown. So, not only does the clinician carry the burden of keeping up to date with advances in genomic related treatments, but they also have to counsel patients on the impact of the testing results on their health and the best course of treatment.

One such class of results in the patient's genome are known variants of unknown significance that may (or may not!) have any consequence for the patient's health. For a clinician, this means delivering results that do not have a clear action, clear meaning, or clear risk associated with them. For the patient, this means receiving information that something is "abnormal" in their results, and yet, the clinician cannot tell them what that abnormality means.

Wynn *et al.*[5] documented the challenge clinicians face in explaining a variant of unknown significance to patients. Often, patients responded with confusion about the implication of the findings for their medical care. One clinician shared how a patient responded: *"They say, 'Wait a minute. Regardless of what this is, you say you found this gene. This gene's causing cardiomyopathy. How can I say this isn't part of his problem?' We're looking at them and we're like, 'Yeah, you're right. We don't know.'"*[5] A number of scientific hurdles should first be passed before this information could be conveyed to clinicians within a technological interface.

Conclusion

As the practice of precision medicine becomes more prevalent in oncology, healthcare technology needs to provide an integrated decision support system to address today's industry challenges at the point of care. Current imitations include a lack of interoperability standards, variations in machine and testing specifications, and information and annotation in the patient report, as well as the analytical capabilities of NGS and genotype/phenotype knowledge. We cite two cases (HER2 and TMB) that illustrate practical example of these concerns.

In the meantime, clinicians will have to continue to search for and review data in separate silos, compile the data, and then interpret a patient's NGS results to determine treatment decisions. All too often, physicians have to account for variations in terms of what is included in the report, and different specifications for testing and/or different machines depending on which vendor is used. Even if interoperable systems exist, until there are standards around measuring and reporting results in the same way, additional context will have to be provided around how vendors are defining and measuring results so that results can be exported out consistently. In Part 2 of this paper (next issue), we will discuss tools and an integrated system that enables a clinician to access information easily and make an actionable decision for treating patients. JoPM

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