

How Data and Informatics Intersect to Enable Precision Medicine to Reach its Full Potential

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Introduction and Background

The practice of precision medicine involves the use and application of patient-specific biomarker information to diagnose and categorize diseases that can then guide more effective treatment to improve clinical outcomes with the least toxicity.¹ In cancer, many new treatments approved by the US Food and Drug Administration (FDA) target specific genomic defects known to drive, or significantly contribute, to the cancer phenotype.² Precision medicine aims to accelerate biomarker-driven targeted therapies to individual patients in a responder population.^{3,4} Early examples of biomarker-driven cancer treatment include hormone-receptor positive breast cancer and *BCR-ABL1* positive chronic myelogenous leukemia.

Genomic testing has transformed the precision medicine landscape by bringing together two medical specialties that are experts in cancer: pathology and oncology. Advancing genetics and genomics in the

clinical space necessitates the cooperation and collaboration of oncologists and pathologists. Systemic cancer treatment is increasingly influenced by a shift from histopathologically-defined disease toward molecularly-defined disease where targeted therapies are prescribed to sub-populations of patients expressing specific genomic variants regardless of tumor origin. Moreover, the rapid pace of development and adoption of biomarker testing with next-generation sequencing (NGS) enables molecular pathology laboratories to develop multiple-gene sequencing panels faster and with less expense.

Precision medicine promises to improve medical care. However, appropriate data exchange and informatics platforms need to be in place, to address the many existing and unforeseen challenges facing care teams and laboratories providing highly complex tests. While many factors contribute to the success of precision medicine programs, we will focus on the role of how informatics facilitates

communication and collaboration at the intersection of oncology and pathology.

The Multifactorial Challenges Facing the Precision Oncology Multi-Disciplinary Care Team

The concept of precision oncology was derived from the introduction of precision medicine by the National Research Council that established the position that patients could benefit from targeted genomics. The constant evolution of the biomarker – “omics” data such as genomics, transcriptomics, and metabolomics – has enabled the investigation and treatment of complex disease and at the same time, introduced the need for a knowledge-guided approach that integrates new information at different levels compared to evidenced-based practice that relies on statistical significance of a treatment applied to a group of patients.³

Treatment planning for patients receiving personalized care such as patients with cancer is

NSCLC Workflow

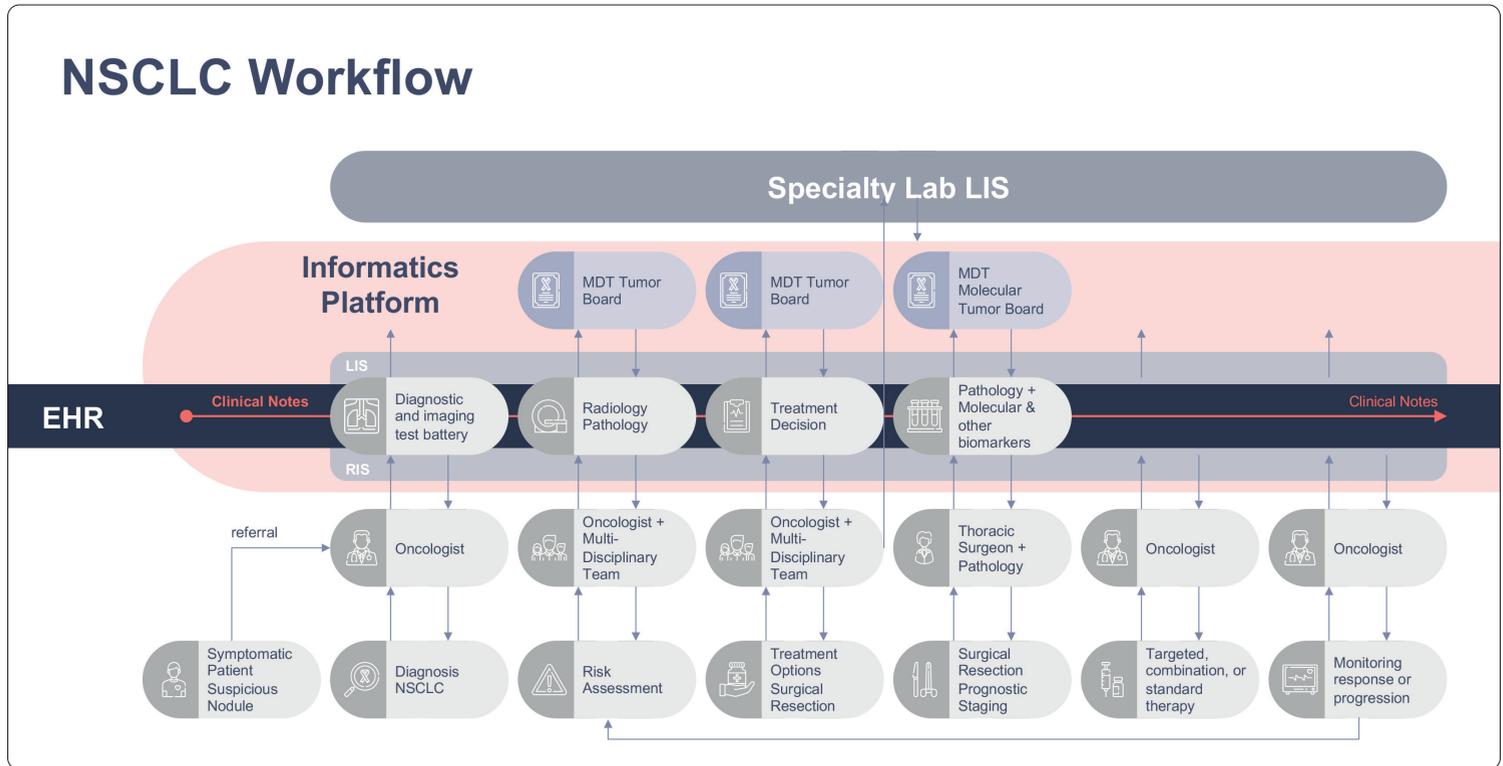


Figure 1: Care process model based on National Comprehensive Cancer Network (NCCN) for non-small cell lung cancer (NSCLC).

not conducted by a single physician but rather, by a team of clinical specialists that rely on each other's expertise to interpret test results and assess risk to develop the best treatment options for the patient. The Commission on Cancer, a program of the American College of Surgeons, has developed standards that focus on improving outcomes through a multi-disciplinary team (MDT) approach to cancer care that is applied in the current care setting.⁵

The same multi-disciplinary team approach is even more important in the precision medicine environment as physicians strive to deliver optimal care, manage risk of cancer-related comorbidities, and ensure knowledge transfer across the entire care team. The challenges for the care team are multifactorial and include: the complexity of interpreting results and translating laboratory data into meaningful information used for treatment planning as illustrated in **Figure 1**. The figure was modeled after NCCN guidelines to the treatment of non-small cell lung cancer and is a representation of the stages of a patient journey including the multi-disciplinary care team (MDT) members, interactions with various health information systems, patterns of communication, and flow of information.

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A recent publication in the *Journal of Clinical Oncology - Precision Oncology* describes the importance of the molecular tumor board in a case study of a 54-year old male diagnosed with microsatellite stable stage II non-mucinous colon adenocarcinoma with no evidence of *RAS* or *BRAF* mutations. After six months of treatment with capecitabine, multiple peritoneal and liver metastases were identified at which time he was referred for additional molecular testing. The NGS results identified a new *ALK*-fusion

in his colon cancer through comprehensive genomic analysis. The interpretation of the results was not obvious and required extensive research into the prevalence of such a mutation and the possibility of a false positive. Alignment of the MDT to include the bioinformaticist to evaluate the results, notably the sequences, rendered a decision to place the patient on a targeted therapy that successfully treated his tumor.⁶

There exists a long-standing disagreement regarding how MDT meetings, such as tumor boards, may, or may not, improve patient outcomes. However, the knowledge sharing and transfer across care team members is invaluable, especially in the current environment of high complexity biomarker testing for cancer.



The Role of the Laboratory and Precision Testing

Laboratory testing is the single highest volume medical activity that drives clinical decision making in PM. As a result, laboratorians and clinicians have the responsibility to match appropriate testing with appropriate therapy.⁷ Unfortunately, the laboratory's contribution to the success of PM has historically been under-recognized. By definition, PM is driven by biomarker data generated in the laboratory, yet stakeholders have done little to improve the delivery, utilization, and access to the wealth of knowledge residing within the laboratory system.

Getting the right treatment to the specific patient at the right time isn't even possible without that patient first getting the correct laboratory test, at the right time, with the results being received by the care team in a timely fashion in an easily assessable and interpretable format. The current system (or lack thereof) is fraught with inefficiencies that contribute to the uncertainty of the value of laboratory testing that in turn, limits the potential success of precision medicine programs. These inefficiencies have a real and significant impact on patient outcomes often resulting in restricted access to potentially beneficial therapies.

Clinicians are faced with navigating the increasing number of biomarker testing options in addition to understanding how and when to order the right test at the right time. The Institute of Medicine identified the need to optimize how genomic diagnostic testing and the resulting information can be integrated into the clinical pathway to maximize patient benefit and minimize harm.⁸⁹ The integration of this type of information can be facilitated through the knowledge sharing process within the MDT but at the same time, requires the thoughtful engagement pathologists with ordering physicians to ensure best outcomes for patients.

Laboratories have the responsibility to develop informatics solutions that facilitate clinical consultation to assist ordering clinicians on the interpretation and the impact of test results beyond just providing a PDF lab report. While PDFs were well suited during the paper documentation era, the content in a PDF is not easily ingested into the clinical workflow of an oncology module in an electronic medical record (EMR) or other healthcare IT system and provides little to no means of computable data.

The Role of Informatics in the Precision Medicine Landscape

Precision medicine informatics is the science



Figure 2: Informatics and knowledge engineering approach to data integration and sharing.

“Recent survey results conducted with the Journal of Precision Medicine and XIFIN, Inc reported that approximately 59% of respondents indicated that their enterprise EMR or EHR did not or only partially met their needs as an end-user.”

of linking computer science, healthcare information, and biology of disease to the individual patient. The application of informatics to precision medicine requires a different approach as technologies are introduced and the data generated in precision medicine initiatives evolves from evidence-based practice into treating the mechanisms of the disease.

Advancements in informatics over the past few decades allowed the development of computer systems to assist with storage, processing, and sharing of healthcare information as electronic health and/or medical record systems (EHR, EMR), laboratory information systems (LIS), and radiology information systems (RIS) were developed and standardized to replace paper charts, and a combination of separate computer programs, spreadsheets, and paper documentation for tracking administrative, pharmacy, and billing records.

The evolution of the EMR allowed for storing data for a patient across time with a focus on care management, improvement of outcomes, and population health. Unfortunately, those very same monolithic healthcare systems were not designed, and cannot scale, to meet the requirements of a learning healthcare system model that integrates biology into a knowledge base to support just-in-time use of clinical-genomic information. Recent survey results conducted with the Journal of Precision

Medicine and XIFIN, Inc reported that approximately 59% of respondents indicated that their enterprise EMR or EHR did not or only partially met their needs as an end-user.¹⁰

The challenges that have contributed to a lack of solutions to meet the needs of precision oncology are partially attributed to the constantly evolving nature of precision medicine. Other contributors include: the complexity and heterogeneous nature of data generated for a variety of tests, lack of true interoperability and therefore, inaccessibility to the patient record data (internally and externally), and continued emphasis on quality (performance-based) requirements in the value-based healthcare landscape.

In the value-based care era, a precision medicine informatics roadmap should be designed and architected from a knowledge engineering approach, by leveraging standards and tools to enable interoperability, thus facilitate turning data into meaningful information. Informatics and data strategies are critical to linking access to information, both internally and externally, through EMRs to physicians, laboratory scientists, pathologists, and bioinformaticists. All stakeholders can benefit from this approach.

Professional societies including, but not limited to the American Medical Informatics Association (AMIA) and American Health Information Management Association (AHIMA)

have identified and published many peer-reviewed manuscripts and opinions on the gaps resulting from the lack of interoperability and the failure of EMRs to meet the new challenges of how PM will be integrated into value-based care models.^{11,12} Communication of clinically relevant genomic findings requires an elevated level of interoperability by leveraging standards associated with a knowledge engineering approach. A knowledge-based approach focuses on seamless integration of systems, people, and processes, and is fundamental to achieving interoperability that significantly affect patient care. **Figure 2** illustrates a knowledge engineering approach necessary to achieve interoperability in PM.

Although there are many factors that will contribute to the success of precision medicine programs, we have identified four areas where an informatics approach is critical for success.

1. **Electronic medical records:** Electronic medical records will be required to extend and scale to meet the growing requirements of precision medicine. To become fully integrated, EMR vendors will have to expand beyond manual upload of documents or PDFs and fully adopt standards to enable content to be produced and consumed from heterogeneous systems and networks. Healthcare systems can already consume pathology/histology through an HL7 message but results from laboratories outside of the health system are not always consumed in an electronic format other than a PDF document.

Traditional EMRs are designed to address some common needs of providers (scheduling, billing, ordering). It is valid to assert that these “traditional systems” provide very important tasks for the day-to-day operations of healthcare organizations, but they fall short when addressing the rapid pace of the current precision medicine needs, because they are not designed to keep up with the pace of new datasets that are being generated by the ever-increasing number of high complexity genomic laboratory tests.

Studies have reported on how EMRs contribute to physician burnout, high job dissatisfaction, and increased stress. One study reported that EMRs and EHRs contribute to burnout from the burden of searching for critical information residing somewhere in a tab within the EMR and EHR, and the clerical burden of charting and cumbersome, and time-consuming

data entry at home during evenings or weekends.¹³ Additionally, The Doctors Company survey reported that 61% of physicians reported EMRs have disrupted the physician-patient relationship, reduced clinical efficiency and lowered productivity.¹⁴ Physicians in the era of PM need to focus on their patients and not searching for NGS results reported in a PDF document that resides in a media tab somewhere buried within the EMR.

2. **Laboratory information systems:**

The nature of precision medicine requires that laboratories become more precision medicine focused.¹⁵ Laboratories that provide advanced NGS assays for use in the clinical setting will need to take a more involved role with the MDT and patient care. The laboratory of today and in the future will need to develop new diagnostic strategies as testing becomes increasingly complex and pricing considerations impact the adoption of new tests. Laboratories generate large volumes of digital data from complex biomarker testing, new test

“With over 75,000 genetic tests on the market in 2017 with 10 new tests being added daily, it is little wonder that uncertainty exists.”

development, and the adoption of digital pathology. Access, retention, and reuse of the data is critical for laboratories to remain competitive. A laboratory focused informatics approach to facilitate data reuse for education, publication, collaboration, and quality assurance is essential.

3. **Interoperability:** The industry has made significant improvements in order to enhance interoperability among heterogeneous healthcare systems in the past few decades. As a result, the HL7 group was established as a not-for-profit organization that has, since 1987, provided standards for healthcare data interoperability and is probably the most well-known name in this area. The most common and widely adopted standards are HL7 version 2 (HL7v2), and HL7 Fast Healthcare Interoperability Resources

(FHIR).¹⁶ The availability and continuous development of existing standards will not address the interoperability challenges, due to the level of data granularity PM requires. The complexity and granularity of the data coupled with the complete lack of communication across vendor systems, the exponential increase and complexity of data that is generated from a single patient, and different sources will magnify the problems of patient/provider data matching, information sharing and flow, and data quality across care settings.

On February 11, 2019, US Health and Human Services (HHS), Centers for Medicare and Medicaid Services (CMS) and the Office of the National Coordinator for Health Information Technology (ONC) proposed new rules to support seamless exchange of electronic health information with the intent to promote access by clinicians and patients.¹⁷ One outcome of the Proposed Rule is to focus on improved interoperability to help patients and physicians make better choices about care and treatment that focus on patient centered health. The added complexity of diagnostics, where the results are generated by an external entity as a static PDF document or worse, in a facsimile will not meet future interoperability requirements or standards. Additionally, clinical care in the precision oncology setting will require further discussion on definition, specification, and implementation of data exchange methods around data sharing in precision medicine programs that can integrate with the EMR/EHR use in precision medicine programs.

4. **Standards:** Health IT data sharing requires the adoption of standards to meet the complex needs of PM and will overlap with new and long-standing standards defined by the National Institutes of Health (NIH) described above and further by the Federal Health Information Technology Standards (FHIT) and the Office of the National Coordinator for Health (ONC).^{18,19,20} Data generated in PM is more complex than data from episodic care and consists of structured and unstructured text, imaging and is subspecialized and multi-modal in nature. Moreover, since patient-level clinical data will need to be tied to biomarker and genomic results not necessarily generated from the same laboratory where the NGS tests were performed, successful data collection and sharing can only be facilitated by adoption of existing standards



