Finding the Evidence in Real-World Evidence: Moving from Data to Information to Knowledge

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Information to guide the delivery of optimal cancer care has traditionally been developed through the conduct of prospective clinical trials sponsored by the National Cancer Institute or by commercial entities, ie the pharmaceutical industry. Results of these trials form the evidence base for clinical practice guidelines, treatment pathways, drug compendia listings, and other care standards that support reimbursement policies and, therefore, access to care. Where evidence from clinical trials is lacking, reimbursement policies and clinical decision-making are typically supported by data from observational studies, tumor registries, or analysis of outcomes derived from insurance claims data. As treatment options for cancer patients continue to expand, all of these mechanisms will likely be necessary to understand how treatments compare, and which treatment works best for which patients. Collectively, the data obtained from sources outside of traditional clinical trials are often referred to as real world data, and the evidence derived from aggregation and analysis of such data as real world evidence (RWE). Real world data typically display the characteristics of "big data," namely, volume, velocity, variety, and veracity, with the latter often presenting the greatest challenge for evidence generation.

CONTRASTING RANDOMIZED CLINICAL TRIALS AND REAL WORLD EVIDENCE

Randomized clinical trials (RCTs) provide the highest level of evidence to establish the efficacy of the intervention being studied. Oncology RCTs conducted by both the academic research community and commercial sponsors have provided data to support the regulatory approval of new drugs or new indications for existing drugs that can potentially cure or improve survival of cancer patients; refine the methods of delivery, scheduling, and dosing of oncology drugs; identify subpopulations of patients who are most likely to benefit (or be harmed) from a specific therapy; and establish the utility of combining different therapeutic modalities to treat patients.[1,2]

Although RCTs have clearly advanced the care of cancer patients, they have significant limitations. An RCT is costly to develop and conduct. The process of developing and activating an RCT is slow and is plagued by a burdensome infrastructure and substantial regulatory oversight.[3] These trials often require large numbers of patients to identify modest differences between treatments and can take years to accrue and reach the primary endpoint being studied. An RCT typically requires complex protocols and collection of large amounts of patient data and documentation, which increases the work load and costs for participating sites. Recent studies suggest that a substantial proportion of phase III oncology trials are never completed, wasting both financial and patient resources.[4] As the treatment of cancer advances and new findings are discovered, the delays in start-up and completion of RCTs may lead to results that are no longer relevant by the time they are reported due to changing standards of care. Furthermore, all RCTs have eligibility criteria in order to define the patient population necessary to address the trial's objectives. Eligibility criteria, by their nature, limit the applicability of the trial results. Therefore, critics of RCTs argue that the patient population studied often does not reflect the "real world" practice of medicine because the inclusion criteria may lead to selection of only the healthiest patients and may exclude patients with medical comorbidities or borderline organ function. So, although an RCT may adequately assess the efficacy of an intervention (ie what can work); the "real world" effectiveness that is seen once the intervention is deployed in community practice (ie what does work) may be substantially different.

In addition, RCTs often evaluate therapies under idealized clinical conditions, including protocol-specified dose modifications and toxicity management; therefore, the results generated from an RCT may not be replicated when the therapy is translated to general practice settings and to real world patients. Furthermore, the efficacy endpoints traditionally used in cancer clinical trials may not reflect outcomes that are most important to patients, such as relief of symptoms, improvement in quality of life, or

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Abbreviations and Acronyms

CER = comparative effectiveness research
EGFR = epidermal growth factor receptor
RCT = randomized clinical trial
RWE = real world evidence

achievement of personal goals. Better measures of these patient-reported outcomes are urgently needed and must be incorporated in clinical trials to better assess the impact and value of a new treatment.

Tumor heterogeneity also challenges the ability to develop new cancer treatments through traditional prospective clinical trials. Because common tumors are often divided into rare molecular subtypes, it is increasingly challenging to identify eligible patients and complete recruitment to clinical trials in a timely fashion. Rates of enrollment of adult cancer patients in clinical trials remain stagnant, at no more than 3% to 5%. With more tumor types, more drugs, fewer eligible patients, and strained research budgets, it is no longer possible to learn everything that still needs to be learned in cancer treatment through the conduct of conventional, prospective clinical trials. These limitations have given rise to interest in the use of RWE to fill knowledge gaps that simply cannot be addressed by conventional clinical trials.

A challenge is to extract information from real world data that provides clinically meaningful and reliable insights that can be applied in patient care. Figure 1 provides an example of a knowledge hierarchy to illustrate progression of data to information to knowledge to wisdom. Detection of the L858R mutation in the epidermal growth factor receptor (EGFR) provides a piece of data that signifies a genomic alteration. The information attributed to this data element is that it represents a DNA mutation that sensitizes tumor cells to EGFR tyrosine kinase inhibitors. The knowledge of how to use these inhibitors comes from clinical studies that demonstrate clinical benefit for lung cancer patients whose tumors harbor these mutations, but the wisdom associated with their use derives from the recognition that not all patients will benefit, and for those who do, the benefit will likely be transient.

It is useful to contrast the strengths and weaknesses of RCTs and RWE, and the advantages and disadvantages of each are depicted in Tables 1 and 2. Advantages of RCTs include collection of data that are complete, accurate, unbiased, and standardized. Disadvantages are the long time and high expense typically required to complete an RCT and the lack of generalizability of the trial data to populations not eligible for study participation. By contrast, RWE has the advantage of capturing the outcomes of patients in the usual practice setting. But studies that rely on RWE are also subject to bias, incomplete or inaccurate data, and use of data elements and outcomes measures that are not standardized across study sites, all of which contribute to concerns about the reliability of the information obtained from analysis of such data sets. The many potential sources of bias in RWE are

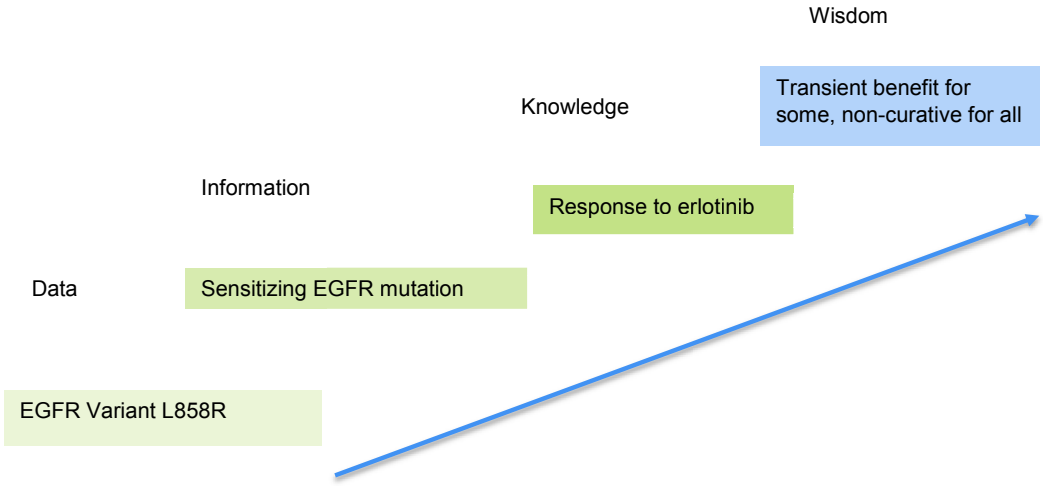

Figure 1. Knowledge hierarchy. Detection of the L858R mutation in the epidermal growth factor receptor (EGFR) provides a piece of data that signifies a genomic alteration. The information attributed to this data element is that it represents a DNA mutation that sensitizes tumor cells to EGFR tyrosine kinase inhibitors. The knowledge of how to use these inhibitors comes from clinical studies that demonstrate clinical benefit for lung cancer patients whose tumors harbor these mutations, but the wisdom associated with their use derives from the recognition that not all patients will benefit, and for those who do, the benefit will likely be transient.

Table 1. Advantages and Disadvantages of Randomized Clinical Trial Evidence

Advantage	Disadvantage
Complete	Slow, costly to obtain
Accurate	Applies only to population studied
Unbiased	Uninformative for older, sicker patients seen in practice
Specified intervention	Control group may not reflect contemporary practice
Standardized outcomes measures	
Reflects "what can work"	

summarized in Table 3, and attempts must be made to minimize such biases in the collection and analysis of real world data.

CancerLinQ: A RAPID LEARNING SYSTEM FOR ONCOLOGY

A series of reports by the National Academy of Medicine (formerly the Institute of Medicine) has called for creation of a rapid learning health care system to improve clinical care.[5] The Institute of Medicine has expressed the view that a learning health care system supports patient-clinician interactions by providing patients and clinicians with the information and tools necessary to make well-informed medical decisions. Such a system can play an integral role in developing the evidence base that supports clinical decisions by capturing data from real-world care settings that researchers can then analyze to generate new hypotheses and insights. Further, it can be used to deliver point of care education and to collect and report quality metrics, implement performance improvement initiatives, and allow payers to identify and reward high-quality care.

CancerLinQ (Cancer Learning Intelligence Network for Quality) is a physician-led initiative representing a fundamental evolution of the American Society of Clinical Oncology's core mission of supporting the delivery of quality cancer care.[6] Designed as an oncology rapid learning health care system, CancerLinQ is a health information technology platform that harnesses the power of big data to learn from every patient. CancerLinQ meets the need for more effective, adaptable, and comprehensive quality improvement tools at the point of care. It compares the process and outcomes of care against the best standards available in order to rapidly feed information back to practices on the quality of care achieved.

Table 2. Advantages and Disadvantages of Real-World Evidence

Advantage	Disadvantage
Captures outcomes of patient in usual practice setting	Subject to bias
Responsive to changes in practice	May be incomplete
Reflects "what does work"	Quality uncertain
Readily available, quickly	Data elements and outcomes measures not standardized; heterogeneous population may mask treatment effect; hypothesis-generating

Table 3. Types of Bias in Observational Studies

Selection bias: inadvertent or intentional differences in selection of patients for treatment
Performance bias: the result of differences in adherence
Detection bias: the result of differential assessment of outcomes
Attrition bias: the result of differences in the groups that withdraw from a study

CancerLinQ gathers data through direct electronic feeds from the electronic health records and practice management systems of participating oncology practices. This obviates the need for manual chart abstraction, making the system more flexible and attractive to providers than existing systems. CancerLinQ attempts to ingest all data contained within the source systems, not just selected fields, and stores the data in a series of progressive databases within the architecture. This results in a far more comprehensive collection of information than that obtained from the extraction of pre-specified data elements, such as those used in traditional cancer registries.

CancerLinQ, currently deployed in more than 70 vanguard practices, enables oncology practices to measure how their care compares with guidelines and with their peers based on aggregated reports of quality, so they may use the information in their own quality improvement process, thereby furthering a culture of self-examination and improvement. CancerLinQ provides clinical decision support to prompt physicians to choose the right therapy at the right time for each patient, based on published treatment guidelines and other knowledge bases. CancerLinQ provides powerful analytic tools that reveal previously unrecognized patterns in patient characteristics, treatments, and outcomes that can lead to improvements in care and suggest new research hypotheses. Insights gained in this process, once verified, have the potential to contribute to a virtuous cycle of learning that ultimately will improve practice guidelines.

The long-term vision for CancerLinQ has a number of additional objectives:

1. Help providers assess patient eligibility for clinical trials and match patients to available trials.

2. Help providers create longitudinal treatment plan documents at the start of an episode of care and treatment summary documents at the conclusion to facilitate communication among members of the health care team and between patients and providers.
3. Improve the signal-to-noise ratio of clinical decision support tools for oncologists by providing clinical decision support that is more specific to the characteristics of individual patients.
4. Improve risk stratification for patients when considering treatment, either standard of care or care delivered in the context of a clinical trial.
5. Monitor the performance and safety of drugs after introduction into routine clinical practice to discover new signals and potentially inform the regulatory process and drug labelling.
6. Assess patient outcomes after off-label prescribing of approved drugs.
7. Generate a longitudinal database of patient-reported outcomes through deployment of a patient portal.

An essential initial step in order to realize the vision of CancerLinQ is the extraction of data from the electronic systems of a participating practice, a process known as data ingestion. CancerLinQ accepts all data in any format that a practice chooses to send. The extract, transform, and load functions in CancerLinQ consist of the following steps and have been described in detail elsewhere[6]:

1. Data extraction. The clinical extract contains common data concepts incorporated into oncology electronic health records. This is a dynamic set of elements, ranging from patient demographics to medication lists to treatment-specific elements such as date of last chemotherapy. The data are extracted from the source systems using a multipronged approach most applicable to the practice site. Each practice is asked to provide any standards-based documents that are currently in use or produced per compliance with Federal meaningful use requirements. Examples include the Continuity of Care Document (CCD), an Extensible Markup Language (XML)-based mark-up standard used for the exchange of patient summaries[7] and the Health Level 7 (HL7) Consolidated-Clinical Document Architecture (C-CDA).[8] Another candidate document is the Clinical Oncology Treatment Plan and Summary (eCOTPS), recently described by Warner and colleagues,[9] the first oncology-specific CDA standard to achieve HL7 Draft Standard for Trial Use (DSTU) status. Customized solutions developed in cooperation with electronic health record vendors may also be used. Most sites will require a combination of these techniques.
2. Data transfer. The practice securely transmits the files to CancerLinQ for consumption.
3. Data load and storage #1. All data received from practices are stored and maintained in the original format in a data lake.
4. Data processing. CancerLinQ moves codified data from the first database ("data lake") to the second (the "processed data"). In this process, the data are standardized and normalized. The knowledge source (content) for the standardization is the NCI Metathesaurus.
5. Ontology services. Custom-built ontology services are implemented at the database level to make them available to several functions, including analytics, data ingestion, and natural language processing. Natural language processing of unstructured data (eg free text fields in a file or text/PDF/Microsoft Word binary documents) will find a "Fact"; eg a Diagnosis Fact or a Biomarker Fact. Here, too, ontologies can be applied to the results of the natural language processing to infer facts and conduct reasoning.
6. Data transfer and storage #2. The data are written to the processed database.

Figure 2 illustrates the general data flow in CancerLinQ and potential points of failure in data extraction, mapping, or harmonization that necessitate implementation of rigorous quality control procedures to insure the CancerLinQ data is suitable for analysis.

CancerLinQ AND CLINICAL RESEARCH

CancerLinQ has the potential to transform clinical research in many ways and to generate information that reliably fills the knowledge gaps that cannot readily be addressed by prospective clinical trials. CancerLinQ will use machine learning algorithms and artificial intelligence to uncover trends in the redacted data sets, such as unanticipated adverse events, which may require further analysis, development, and exploration.

A significant proportion of oncology drug use is for an indication that is not reflected on the FDA-approved label. Although such off-label use is often sound medical practice, it can be based on small studies and even case reports. There is no organized system to aggregate these experiences and understand what actually works and in what setting. CancerLinQ will be able to supply this information to enable more comprehensive and in-depth analysis of off-label uses and associated patient outcomes. Variables such as age, sex, comorbid conditions, current medications, specific organ function, performance status, and

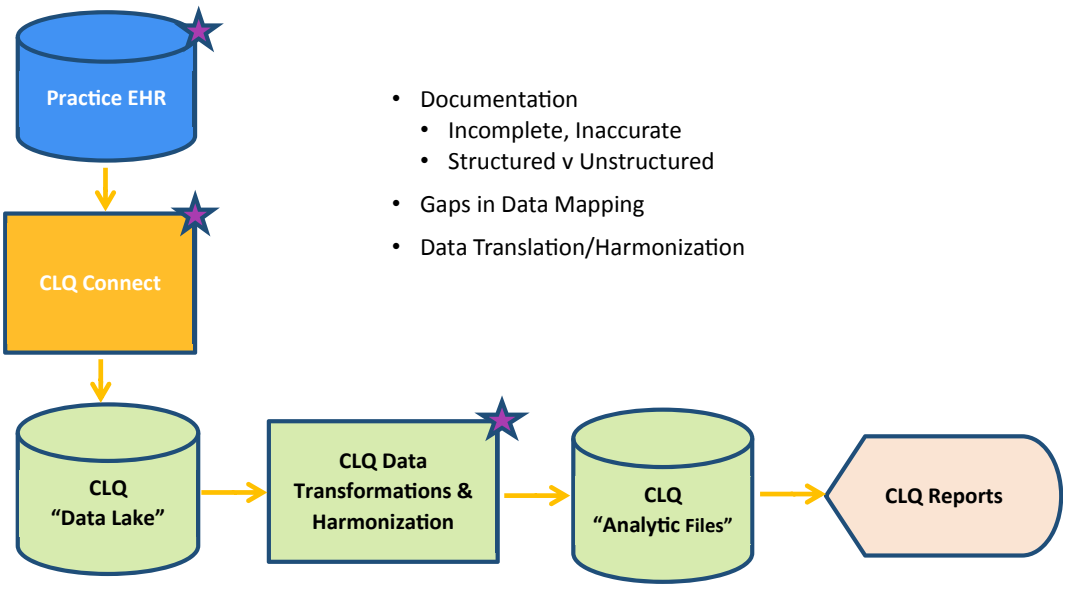

Figure 2. CancerLinQ data quality: potential points of failure. General data flow in CancerLinQ and potential points of failure in data extraction, mapping, or harmonization (indicated by stars) that necessitate implementation of rigorous quality control procedures to insure the CancerLinQ data is suitable for analysis. CLQ, CancerLinQ; EHR, electronic health record.

a host of other factors influence cancer outcomes. Increasingly, molecular characteristics will be incorporated into risk stratification schemes. CancerLinQ will be able to analyze tens or hundreds of thousands of cases and produce findings that enable treating oncologists to begin to risk stratify patients with far more precision, hopefully leading to better selection of therapy and improved patient outcomes.

CancerLinQ will enable the monitoring of safety and efficacy signals in real world populations, overcoming the current limitations of drug registration trials, which often treat patient populations not representative of patients in practice, who are often older, with a higher number of comorbidities.

CancerLinQ will make redacted data sets available for research activities pursuant to established policies and procedures. Where appropriate, individual investigators will be able to propose specific research questions for review and approval, and the system will use the redacted data sets to generate either a report or a data set necessary to address the question. CancerLinQ can also be a data source for registry-driven RCTs and comparative effectiveness research (CER), defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels."[10] Research that is compatible with the aims of CER has 6 defining characteristics:

1. The objective is to inform a specific clinical question.
2. It compares at least 2 alternative interventions, each with the potential to be a "best practice."
3. It addresses and describes patient outcomes at both population and subgroup levels.
4. It measures outcomes that are important to patients, including harms and benefits.
5. It uses research methods and data sources that are appropriate for the question of interest.
6. It is conducted in settings as close as possible to the settings in which the intervention will be used.

The utility of RWE in CER is illustrated by a comparison of the RCT data for laparoscopic colectomy with the RWE that chronicles its use in practice. The Clinical Outcomes of Surgical Therapy (COST) trial clearly established that laparoscopic colectomy, performed under the rigid controls and procedures of a prospective RCT, results in recurrence and survival outcomes that are indistinguishable from those obtained with conventional open colectomy for patients with resectable colon cancer.[11] The COST trial results were published in 2004 and in

the ensuing years, laparoscopic colectomy was deployed in clinical practice. In 2008, an analysis of outcomes for laparoscopic colectomy culled from the National Cancer Database was published, and it confirmed similar outcomes for colon cancer patients treated with laparoscopic or open colectomy.[12] However, the actual survival observed for patients in the National Cancer Database treated with laparoscopic colectomy was inferior to that obtained in the COST trial (5-year overall survival of 64.1% vs. 76.4%, respectively), illustrating a common discrepancy between clinical trial outcomes and clinical practice outcomes likely due to greater heterogeneity in patient selection and application of the treatment in the practice setting.

It is expected that CancerLinQ data will support similar analyses in the future. For example, at the 2016 American Society of Clinical Oncology annual meeting, investigators reported that patients with metastatic colorectal cancer treated in a clinical trial had different treatment outcomes depending on the site of origin of the primary tumor, with tumors originating on the left side of the colon having more favorable outcomes, particularly when treatment included chemotherapy plus cetuximab rather than chemotherapy with bevacizumab.[13] An analysis of more than 11,000 patients in the CancerLinQ data performed at the same time revealed that the great majority of patients with left-sided colon tumors had received treatment with chemotherapy plus bevacizumab, the prevailing standard of care. This observation now provides a baseline against which to assess changes in practice trends and patient outcomes after the reporting of the clinical trial data.

IMPROVING THE EVIDENCE DERIVED FROM REAL WORLD DATA

The utility of real world data to generate clinically useful information depends to a great extent on the quality of the source data that feed registries and learning systems. At the present time, many important oncology clinical endpoints, such as response and progression events, are not captured as standardized, structured data elements and can only be extracted from clinical notes by manual curation or natural language processing. Expansion of structured data reporting of key oncology endpoints within electronic medical records could greatly remedy this problem and should be strongly encouraged, along with structured reporting of pathology and radiology findings. If accompanied by comprehensive training of data entry staff in the clinical environment, the key endpoints necessary to assess cancer treatment outcomes would be much more readily identifiable and extracted from electronic medical records for collection in data registries. Improving electronic medical record interoperability and prohibiting data blocking by proprietary entities will also facilitate data collection from multiple care settings. Eventually, natural language processing and machine learning capabilities will improve and further enhance the extraction, analysis, and reliability of real world data.

CONCLUSIONS

In view of the enormous heterogeneity of cancer and the complex and multidisciplinary nature of cancer care, it is simply no longer possible to learn everything that remains to be learned about cancer care from prospective clinical trials. There are simply not enough patients, time, or money to examine every open question in cancer care with clinical trials. Real world data derived from capturing the longitudinal experience of each cancer patient provide an enormous opportunity to fill knowledge gaps, provided that the information derived from analysis of that data is reliable, reproducible, and informative to guide clinical care, that is, provided that we can convert data to knowledge and, eventually, to wisdom. The over-arching goal of CancerLinQ is to enable oncologists to learn from every encounter with every cancer patient and to rapidly gain insights that can benefit all cancer patients. Realizing this vision will rapidly accelerate knowledge acquisition and improve the overall quality of cancer care.

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