CellPress

Opinion

Cancer Genomics in Clinical Context

Lynda Chin,[1,*] Jennifer A. Wargo,[1,2] Denise J. Spring,[1] Hagop Kantarjian,[3] and P. Andrew Futreal[1]

Precision medicine requires appropriate application of genomics in clinical practice. In cancer, we have witnessed practice-changing examples of how genomic knowledge is translated into more tailored and effective therapies. The next opportunity is to embed cancer genomics in clinical context so that patient-centric longitudinal clinical, genomic, and molecular phenotypes can be compiled for adaptive learning between precision medicine research and clinical care with the goal of accelerating clinically-actionable discoveries. We describe here an adaptive learning platform, APOLLO™ (adaptive patient-oriented longitudinal learning and optimization) designed to integrate genomic research in the context of, but not in the path of, routine and investigational clinical care for purposes of enabling data-driven discovery across disciplines such that every patient can contribute to and potentially benefit from research discoveries.

Trends

Because the cancer genome evolves during disease progression and treatment, longitudinal characterization linked to clinical information is important for understanding how genomic insights can inform and improve care.

Science is not equivalent to medicine. Thus, a system that integrates genomic research in context, but not the path, of clinical care is much needed.

APOLLO is a platform developed to enable cancer genomic research during routine and investigational care.

To learn from every patient (N-of-ALL), and to harness the power of big data, APOLLO implements standardized and systematized processes to obtain patient consent, collect samples, generate and aggregate research and clinical data across disciplines to accelerate translation of cancer genomic insights into precision-medicine practice.

Evolution of the Cancer Genome

Concerted efforts nationally and internationally [1–5] over the past decade have endowed the field with a foundational understanding of cancer genomes in the form of a catalog of somatic genomic alterations from primary untreated tumors, including single-nucleotide mutations, copy-number aberrations, and structural rearrangements, as well as epigenomic alterations [6]. However, we have learned that somatic cancer genomes evolve during disease progression [7–9] and adapt in response to treatments [10–15], and therefore the static snapshots produced to date do not adequately provide a complete view of the cancer genomes, not to mention that our understanding of the sequences and their biological or clinical relevance is limited to less than 1% of the genome. Therefore, it stands to reason that impactful applications of genomics in cancer care will require a dynamic view of the cancer genome that is associated longitudinally with disease biology.

The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC) have been the defining projects of the cancer genomics era. Their impacts rest on the creation of high-quality and comprehensive (up to date) genomic references that not only will lead to the identification of promising therapeutic and diagnostic targets but also will drive fundamental discovery in cancer genetics and genome biology. However, TCGA and ICGC are inherently limited in that the focus has been singular: in-depth but static characterization of primary untreated cancers selected from retrospective cohorts. By design, they have not captured the dynamic evolution of cancer genomes that is driven by their extreme adaptability in the context of disease progression and treatments. As these efforts continue, cancer genomics must go beyond mining existing data or expanding the corpus of reference genomic data repositories in isolation of rich phenotypic annotation.

The next step, and indeed the next opportunity to exploit genomic information, will be to put cancer genomics in the appropriate clinical context to generate contextualized genomic data

[1]Department of Genomic Medicine, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA
[2]Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA
[3]Department of Leukemia, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

*Correspondence: lchin@mdanderson.org (L. Chin).

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that can be used to accelerate precision-medicine research for clinically-actionable discoveries [16]. In other words, we need to establish comprehensive longitudinal genomics–phenomics (genotype–phenotype) correlations over time in a patient-centric manner. This means linking serial cancer genomic profiles with longitudinal phenotypic data derived from both clinical care and cutting-edge research on a patient during the entire episode of care (and eventually before and after). We have already witnessed the power of such serial genomic profiles linked to clinical information in the identification of resistance mechanisms to small-molecule anticancer drugs in the clinical setting [13,17–21].

Although we are in grateful receipt of broad catalogs of somatic mutations for the majority of human cancer types, it is readily apparent that there exists a long 'tail' in the prevalence distribution of infrequently mutated cancer genes and relevant genomic aberrations. The mutations and genes on the tails of the distribution may be no less important or clinically informative on an individual patient basis than those that are more frequently identified. Therefore, unless longitudinal genomics–phenomics profiles across time, and in the context of detailed clinical data, are captured for each and every patient, there will be high likelihood that such ubiquitous features of adult solid tumors will be missed from an individual patient perspective. Importantly, such a systematized N-of-ALL approach creates a true learning system that captures insights from each patient, not only those being followed in clinical studies, but also those being treated with standard of care at an institution and in a real-world environment.

In summary, we should adopt an 'N-of-ALL' approach, where 'N' (the number of study participants) includes all patients, to generate standardized and comprehensive longitudinal genomics–phenomics profiles on every patient undergoing clinical care, and make such aggregated patient big data available to diverse clinical and genomic researchers, not only those who have cared for the patients or have been involved in the process of sample collection and data generation. This N-of-ALL approach to comprehensive longitudinal genomics–phenomics profiling transcends our current model of limited genomic (or research) data being acquired at a single point in time from a preselected subset of patients, without linked clinical care information. We believe that such a shift in both thinking and culture is necessary to accelerate genomics discovery and application in precision medicine.

APOLLO, Enabling Cancer Genomics in Clinical Context for Every Patient

APOLLO, an adaptive learning platform developed at MD Anderson Cancer Center, enables cancer genomics in clinical context for every patient such that each can ultimately contribute to our knowledge base to accelerate discovery and translation of genomic insights into new and improved standards of care. To achieve this goal, APOLLO attempts to address some of the key challenges in today's model, particularly the culture of individual 'ownership' of patient samples or data, under-resourced and non-standardized workflows, and the dearth of technology enablement.

Today, conducting clinically-relevant genomic research generally involves a specific protocol with a defined question and limited scope of exploration. Retrospective patient samples are accessed from tissue banks derived from various sources under varying conditions with little or no pathological (re)review. Prospective tissue collection is defined by a specific protocol, that is more likely to receive uniform pathology review and quality control, but which is inherently constrained by the types of data that can be generated. Most commonly, samples are anonymized and thus linkage to clinical data is explicitly broken. To retrospectively annotate research data with clinical correlates requires navigating through a complex matrix of clinical stakeholders, as well as manual data abstraction on a per-medical record basis, a process that is subjective and difficult to standardize. While the backbone of current work, this is essentially an one-off per-hypothesis approach that, even if successful, does not readily allow for re-use and