Personalized care for the oncology patient

Howard J. Lim[1]; Marco Marra[2]; Janessa Laskin[1]
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Cancer is a disease of alterations within a person's genome leading to unregulated growth.[1] By understanding these growth pathways, it is possible to use this information to select drugs that might be beneficial for treatment. Chemotherapy, in general, is therapy that targets various growth mechanisms; furthermore, oncologists have been using personalized chemotherapy care for over a decade. An early example is the use of trastuzumab in HER2–positive metastatic breast cancer that has transformed the treatment of this type of cancer.[2] More recently, advances in gene sequencing technology have seen genomic tumour profiling become more accessible. The paradigm of molecular targeted therapy became reality with the use of imatinib in chronic myeloid leukemia following the discovery of the BCR–ABL fusion.[3] However, the information gained from most genomic profiling technology remains largely experimental and invalidated.

Genomic technology has advanced through the use of next generation sequencing technology. The concept of profiling tumours and normal tissues in clinical settings is not new and has progressed to the point where such profiling has now entered routine clinical care in several jurisdictions including the Memorial Sloan Kettering Cancer Centre[4] and the use of the OncoPanel at the British Columbia Cancer Agency (BCCA) genomics lab (www.ccgenomics.ca). Many clinical–and consumer–based tests use panels that target specific mutations. Panels are populated with mutation or gene targets that are selected based on their known clinical relevance. This provides limited information, but is quick and reliable. Whole genome sequencing (WGS) is more detailed, looking at the entire genome instead of a specific site of a known mutation. While WGS provides more information, data analysis is more time–consuming. WGS also yields variants that might not yet be described and would therefore have unknown significance.

In addition to the OncoPanel, the BCCA and Genome Sciences Centre also enrolls patients into an ongoing clinical trial known as the Personalized OncoGenomics Program (POG). This analyzes whole genome and transcriptome sequencing from fresh tumour samples to provide detailed genomic reporting in the hopes of providing personalized treatment (Figure 1). Understanding the genomic biology, using transcriptome sequencing integrated with genome data, will substantially enhance the sensitivity of detecting actionable alterations and will hopefully reveal therapeutic targets that remain cryptic to panel sequencing. In addition, germline testing will provide a more efficient means of identifying familial risk factors for developing cancer based on hereditary panels, resulting in improved counseling for prophylactic strategies.

The goal of these personalized tests is to gain a detailed understanding of the pathways that can drive a cancer's growth, leading to the identification of biomarkers that can aid in treatment decisions (predictive factors) or estimate a person's survival with the disease (prognostic factors). The research community has continued to

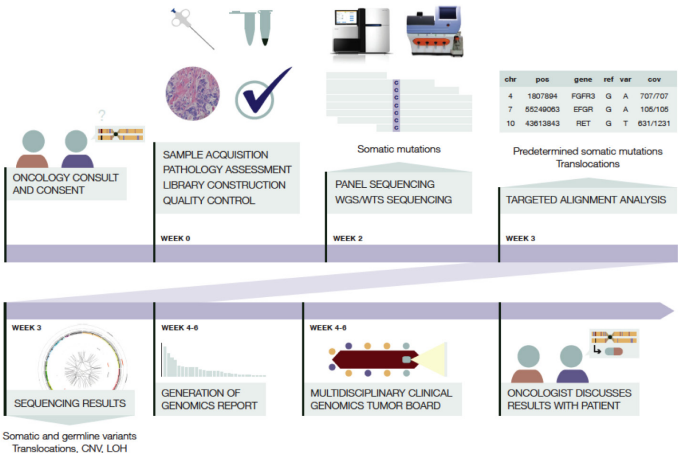

Figure 1 | Personalized OncoGenomics Timeline

provide novel markers that are being validated prospectively in clinical trials. Many of these biomarker–driven trials are breaking away from the hypothesis model of tumour site specificity and moving towards biomarker specificity.[5] One example is the upcoming Canadian Profiling and Targeted agent Utilization tRial (CAPTUR), a phase II basket trial, hypothesizing the presence of a molecular marker will predict the response to target therapy, for patients with incurable metastatic solid tumours. If a tumour has a genomic variant known to be a target of, or to predict sensitivity to, a Health Canada–approved anticancer drug these patients will be eligible to treated with targeted therapies based on the genomic variant and the specific tumour type (Figure 2). The clinical trial protocols will then be used to determine if a person's cancer is responding to treatment.

The caveat to this explosion of bioinformatics is that the majority of discoveries remain largely non–validated. Mutation in or expression of one growth pathway can prove to be predictive in one tumour site, but might not hold true in another. The site of disease biopsy is also key, as a metastatic lesion will have a different profile from primary tissue. Another unfortunate consequence of this technology's progression has led to direct–to–consumer commercial marketing for genetic testing. This is done largely out of context to a patient's history and a

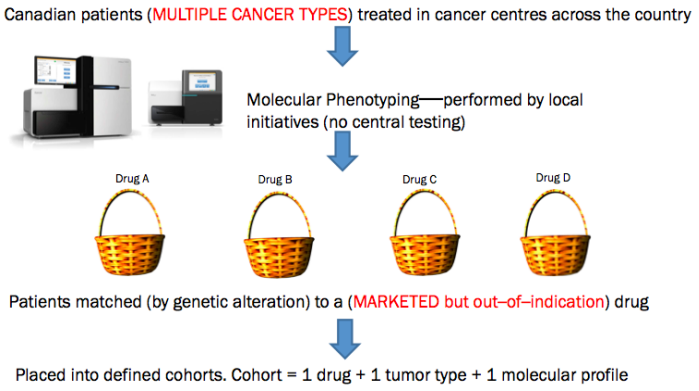

Figure 2 | CAPTUR Study Design

[1]Personalized OncoGenomics Program, Department of Medical Oncology, BC Cancer Agency, Vancouver, BC, Canada
[2]Genome Sciences Centre, BC Cancer Agency, Vancouver, BC, Canada

Correspondence to
Howard J. Lim (hlim@bccancer.bc.ca)

report is generated and left to the unsuspecting physician to interpret. The disease process is made up of both genetic and environmental risks and genomic information obtained without the proper context tends to be confusing and misleading for both physician and patient.

Given that most of these genomic data are largely experimental and should be analyzed in the context of a person's disease process, the use of consumer testing should be discouraged at present. Efforts to validate markers for therapeutics should be done in the context of clinical trials, and the data are largely hypothesis generating rather than hypothesis testing. While the goal of personalized medicine based on sequencing appears to be attainable, treatment decisions based on non-validated genomic information should be done with an extensive discussion with patients about the pitfalls of using non–validated markers.

As we continue to understand more about tumour biology, more therapies will be developed and treatments will be tailored for patients. This learning has extended beyond the oncology arena and will undoubtedly affect other areas of medicine, leading to a paradigm shift in how we treat patients in the future.

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