Chapter 1
Between Hype and Hope, on the Cutting Edge of Precision Cancer Medicine

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The concept of precision cancer medicine emerged with a National Academics of Science report in 2011 describing the need and opportunity to classify human disease through a precision taxonomy. This new taxonomy would be based on the availability of genomics data and other sources of big data to enable a more precise diagnosis and management of human disease. Since cancer is characterized by somatic and germline genetic changes, precision medicine has taken a natural direction that has included clinical oncology. This text includes contributions from leading researchers in the emerging and changing field of precision cancer medicine.

The discovery and characterization of biomarkers and their inherent biology has been dependent on clinical observations and concurrent technologies to study cancer biology. While next generation sequencing (NGS) technologies has been the main accelerator for the identification of biomarker targets or vulnerabilities and the development of matching therapies, there were early examples that predated NGS. This includes the estrogen receptor in breast cancer where patients with metastatic breast cancer serendipitously benefited from hormone deprivation with oophorectomy. Subsequent biomarkers were discovered through early approaches for chromosome analysis including cytogenetics to identify and classify hematologic malignancies such as acute promyelocytic leukemia (t,15;17 translocation involving the retinoic acid receptor) and chronic myeloid leukemia (BCR-ABL1 translocation or Philadelphia chromosome). The development of polymerase chain reaction, FISH, and microarray were concurrent with the discoveries of the

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Epidermal Growth Factor Receptor (EGFR) mutations in lung cancer and HER2 (ERBB2) amplification in breast cancer, which are sensitive to corresponding targeted therapies. However, what these technologies in the laboratory lacked was the scalability, affordability, and speed needed to characterize thousands of patients in the clinic for individualized or precision cancer care.

Around 2010, next generation sequencing technologies accelerated large-scale projects to study the most common cancer types through international efforts including The Cancer Genome Atlas and International Cancer Genome Consortium. These efforts helped to identify the landscape of genomic, epigenetic, and transcriptomic alterations in cancer. Advances in technology and drug development have accelerated the time between "target discovery" to "first patient treated in a clinical trial" (Fig. 1.1). Further, these studies described the vast inter-patient genomic heterogeneity that exists in each cancer type. This illustrated the need for individualized characterization of each patient's cancer in the clinic and that there is no routine cancer.

In 2011, there were early efforts to bring NGS approaches to patient care in real-time and this has led to new questions being addressed through clinical and research efforts:

- How do we characterize one person's cancer?
- Should we get new biopsies? Does cancer change over time?
- Should we sequence the whole genome, the exome, targeted exome, or RNA?

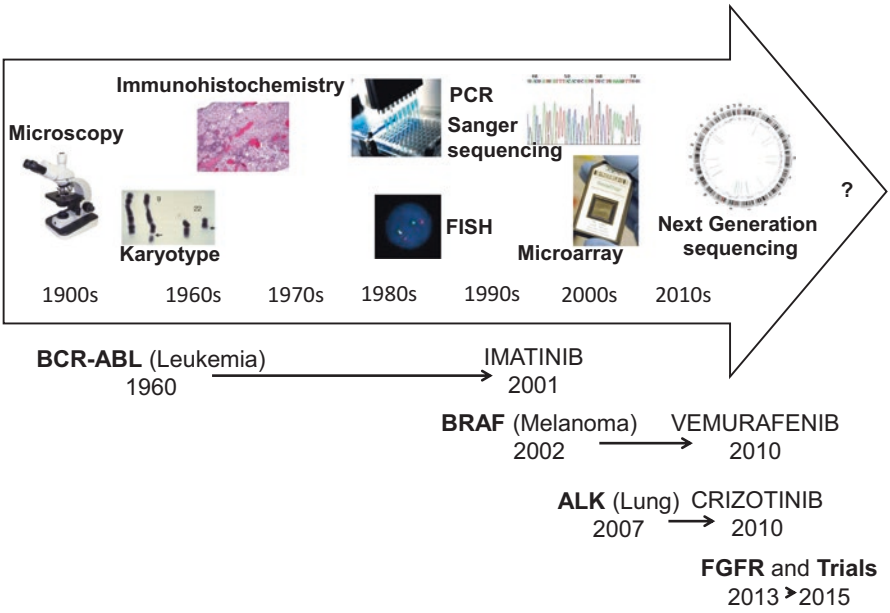

Fig. 1.1 Technology advances precision oncology. This timeline compares advances in genomic technologies and drug development timelines for novel targets in cancer

- What is the best way to analyze this data? Which algorithm is better?
- How do we interpret somatic findings of unknown significance?
- How do we develop and deliver clinical grade diagnostics? What are ideal positive and negative controls? How many?
- What constitutes a proper analytic validation of an assay?
- Are all commercial and academic tests the same quality for point mutations? Amplifications? Fusions?
- Where do store this data? How do we share this data?
- How do we report these results to physicians? What should reports look like?
- How do we connect genomic results to eligible therapies or clinical trials?
- How should we design clinical trials for patients with rare mutations?
- How do we develop and approve new therapies for patients with rare mutations?
- How can we learn from rare patients with an exceptional response to therapy?
- How do connect genomics data to the electronic medical record?
- How do interpret and manage germline findings?
- How do connect genomics data to clinical outcomes?
- How does genomics influence immunotherapy?
- How can we use genomics to study drug resistance?
- How do we speed up genomic testing in the clinic?
- How do we educate our physician workforce?
- Can we connect genomics data to prognosis for indolent and aggressive cancer subtypes?
- Can we use liquid biopsy from the blood instead of tumor tissue?
- What is the concordance of somatic alterations in blood and tumor tissue?
- How do we study clonal hematopoiesis?
- How do get more patients on clinical trials? Or
- How do we characterize patients with no driver mutations or quite genomes?
- How do we bring genomics to health care sites where resources are scarce?
- Why are only 10% of patients who undergo genomic testing able to receiving matching targeted therapies?

There are many answers and ongoing efforts to address these questions. Importantly, there are patients living longer, benefiting from therapy, and even cured thanks to precision cancer medicine approaches. This textbook covers a range of topics from basic science to clinical application for patient care to help describe these solutions and the new problems we need to solve to deliver precision cancer medicine.