

# Next-Generation Sequencing (NGS): Revolutionizing Patient Care in Your Oncology Practice



# Next-Generation Sequencing (NGS) in clinical practice

## Personalized Medical Care: Addressing the Unmet Need for More Precise Treatments in Patients with Cancer

The age of personalized medicine, driven by the capabilities of **Next-Generation Sequencing (NGS)**, is here!<sup>1</sup>

The term *personalized medicine* describes medical advances and approaches based on the analysis of an individual's genomic information. In other words, the genetic information of any given patient is used as part of their clinical care to help predict how they will respond to a given treatment regimen.<sup>2-4</sup>

Personalized medicine has the potential to offer new possibilities: from prediction of a patient's cancer risk to earlier diagnoses and development of novel targeted therapies.<sup>3,4</sup> In order to translate a patient's genomic information in a clinically meaningful way, it is essential for oncologists to become acquainted with the capabilities of NGS and how it can facilitate personalized medicine in their clinical practice.<sup>5</sup>

### What is NGS?

For over 10 years, NGS has been an integral component of translational cancer research in the laboratory. Now, it is becoming more available as an essential tool for the oncologist's armamentarium. The results of new genetic discoveries using NGS technology are enabling more precise decision-making in oncology clinical practice, including patient risk assessment, diagnosis, prognosis, targeted treatment choice, and selection of novel agents in the case of drug resistance.<sup>1,6,7</sup>

Traditional laboratory testing techniques (see **Figure 1**) can provide useful information. However, given today's standards, they are limited in their capabilities and turnaround times.<sup>8</sup> Immunohistochemistry (IHC),

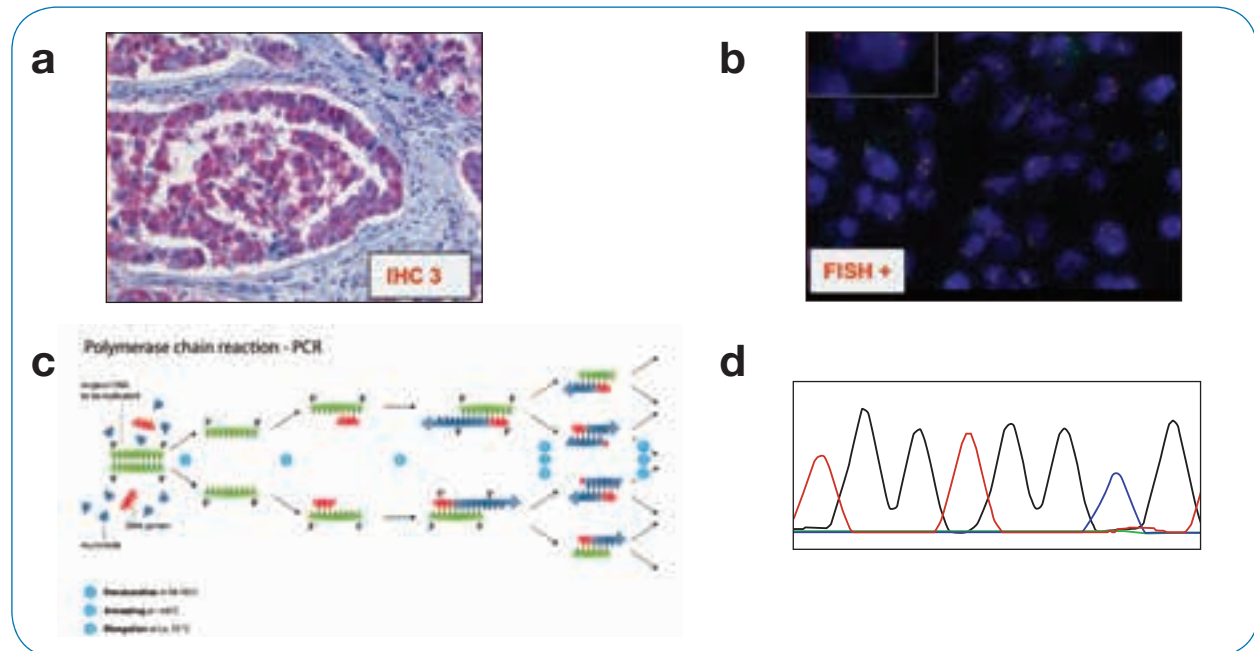


Figure 1. Traditional laboratory cancer testing techniques: (a) Immunohistochemistry (IHC); (b) fluorescence in situ hybridization (FISH); (c) polymerase chain reaction (PCR); and (d) Sanger sequencing. (a) and (b): Reprinted by permission from Macmillan Publishers Ltd: Dietel M, et al. *Cancer Gene Ther*. Advance online publication, 15 March 2013; DOI: 10.1038/cgt.2013.13., copyright 2013; (c): Wikimedia Commons Contributors. "Polymerase chain reaction." *Wikimedia Commons, the Free Media Repository*. November 27, 2016. [https://commons.wikimedia.org/wiki/File:Polymerase\\_chain\\_reaction.svg](https://commons.wikimedia.org/wiki/File:Polymerase_chain_reaction.svg); and (d): Reprinted by permission from Elsevier Inc: Tsiatis AC et al. *J Molec Diagn*. 2010;12(4):425-432.<sup>11-13</sup>

fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR) can analyze small numbers of tumor markers by searching for known “hotspots”: those genetic loci known to frequently mutate.<sup>7</sup> Sanger sequencing, the historic gold standard, can detect single nucleotide variations (SNVs) and small insertions and deletions, but cannot sequence multiple types of genetic alterations or simultaneously screen for multiple genes in a single assay.<sup>8-10</sup>

None of these traditional methods are scalable or capable of high throughput, making them unable to address the ever-growing numbers and varieties of genomic changes occurring in most types of cancer.<sup>9,14</sup> As more clinically relevant mutations are discovered, single-gene assessment by traditional methods are expected to become less feasible over time.<sup>1</sup>

The breakthrough innovation of NGS is the performance of high-throughput sequencing—the ability to sequence millions of small DNA fragments in parallel.<sup>9</sup> In essence, NGS can analyze more detailed information about the molecular makeup of a tumor than any previous technology, essentially offering a “one-stop shop” for currently known targetable mutations.<sup>1</sup> NGS has also become more cost- and time-efficient than traditional methods over the past several years.<sup>1,15</sup>

Following sequencing, bioinformatics assembles these enormous numbers of DNA sequences by mapping each individual read back to the human reference genome, analyzes the variant information through analysis pipelines, then issues a report summarizing the clinical implications of the identified abnormalities (see **Figure 2**).<sup>9,16</sup> NGS can sequence the entire genome multiple times during a single run. With this higher “depth of coverage,” NGS can tackle cancer’s complexity by generating highly accurate data on mutations occurring at low frequency.<sup>7,9,16,17</sup>

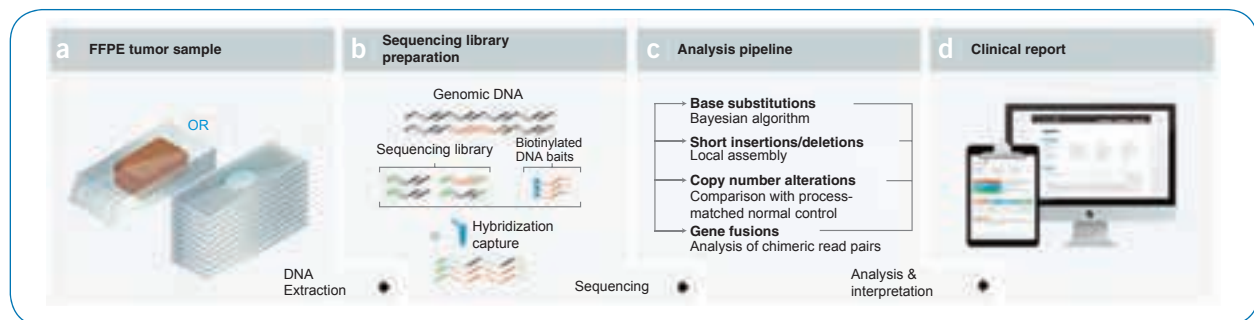


Figure 2. NGS-based cancer genomic profiling test workflow. Reprinted by permission from Macmillan Publishers Ltd: Frampton GM, et al. *Nature*. 2013;31(11):1023-1033, copyright 2011.<sup>14</sup>

For example, a patient’s genome might have more than 1 SNV, structural changes such as small insertions, deletions, and fusions.<sup>6,7,17</sup> NGS can detect these genomic changes in therapeutically relevant cancer genes and do so with a high degree of confidence and accuracy.<sup>7</sup> At a cost of about \$1000 per genome, the massively parallel nature of NGS is a more cost-effective approach compared with Sanger sequencing, in addition to its ability to sequence multiple genes at higher coverage, increase the number of targets per run, and generate up to 6 terabytes (TB) of output in some systems.<sup>15,18</sup> NGS also requires less DNA per assay (in nanogram amounts), dramatically improving the diagnostic yield in clinical samples—especially those very small, invaluable, formalin-fixed paraffin-embedded (FFPE) tumor samples.<sup>6</sup> These NGS capabilities are helping bring to reality personalized treatment of patients with cancer.

# NGS is changing cancer classification

## Key Fact No. 1

Traditionally, tumors have been classified through histology. However, morphology alone cannot detect the mutational signatures that have been shown to be crucial in the development of these tumors (see **Figure 3**).<sup>7,19,20</sup> Now, NGS can generate a molecular profile of many different types of cancers using a very small sample amount, and this is leading to more accurate diagnosis, classification and prognostication, improved treatment selection, and potentially, better disease management.<sup>7,19,21,22</sup>

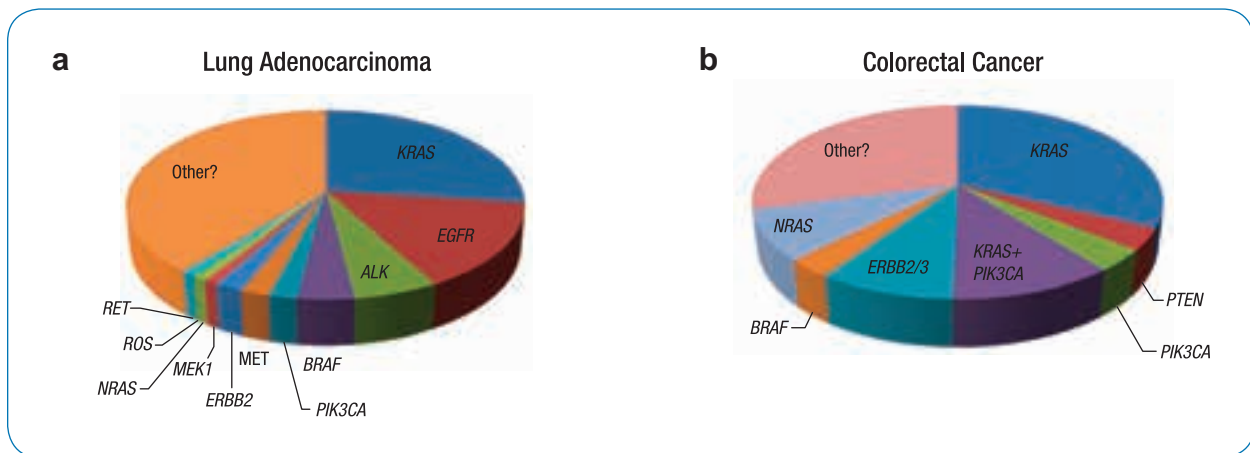


Figure 3. Genomic changes are common in cancer and may drive disease progression. These pie charts identify common genomic changes in (a) lung adenocarcinoma, and (b) colorectal cancer, which may warrant the use of targeted therapies either approved by the US Food and Drug Administration, or currently in development and undergoing clinical trials. “Other?” represents the percentage of driver mutations with no druggable targets. Adapted from Garraway LA. Genomics-driven oncology: framework for an emerging paradigm. *J Clin Oncol.* 2013;31(15):1806-1814. Reprinted with permission. © 2013 American Society of Clinical Oncology. All rights reserved.

In this revolutionary era of genomic medicine, new biomarkers are emerging that may predict a given patient’s anticipated treatment response and outcome.<sup>20,23</sup> Specifically, a *predictive* biomarker helps identify the type of patient who may be more likely to respond to a specific treatment (ie, targeted therapy). A *prognostic* biomarker provides information about the likely outcome for a patient with a given disease (ie, survival rate).

For example, one of the best studied solid tumors is non-small cell lung cancer (NSCLC).<sup>22</sup> Molecular testing for mutations in the epidermal growth factor receptor (*EGFR*) has become the standard of care prior to initiation of tyrosine kinase inhibitors (TKIs, such as erlotinib) that can typically lead to a higher response rate and longer progression-free survival (see **Figure 4**).<sup>22,24,25</sup> In a single run, the enhanced capability of NGS to detect *EGFR* and other causative mutations may not only predict a patient’s sensitivity to a specific treatment, but also their potential for developing drug resistance.<sup>22,25</sup> Molecular profiling using solid and liquid biopsies,

and the ability to target novel endpoints for efficacy (such as dynamic changes in *EGFR* mutations in plasma) will no longer be just the future of health care, but will soon become integrated into the management of patients with cancer.<sup>24</sup>

Metastatic colorectal cancer (mCRC) provides another example of the importance of biomarker testing. In mCRC, mutations in the rat sarcoma (*RAS*) genes (*KRAS* and *NRAS*) are predictors of resistance to monoclonal antibodies that target *EGFR*. Such therapies should only be initiated in those patients who do not have mutations within these *RAS* genes, as confirmed by molecular profiling.<sup>27</sup> Many societies, including the American Society for Clinical Pathology, the College of American Pathologists, the Association of Molecular Pathology, and the American Society of Clinical Oncology, recommend extended *RAS* testing that includes genetic screening of exons 2, 3, and 4 of both *KRAS* and *NRAS* in patients with mCRC.<sup>23,27</sup> NGS has the potential to simultaneously detect all of these mutations in a single run.<sup>23,24</sup>

Compared with traditional mutational screening methods, medical genomics powered by NGS is allowing practitioners to more accurately quantify a patient's prognosis, anticipate their response to treatment, and identify tumors with more aggressive features. As a result, more precise treatment plans can be developed that may help improve patient outcomes by avoiding unnecessary or ineffective therapies, and potentially decrease the occurrence of adverse events (see **Figure 5**).<sup>20</sup>

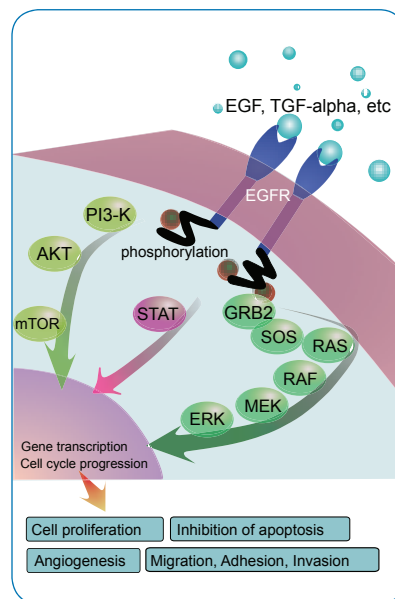


Figure 4. The *EGFR* signaling pathway. Wikimedia Commons Contributors. “EGFR signaling pathway.” *Wikimedia Commons, the Free Media Repository*. September 5, 2015. <https://commons.wikimedia.org/w/index.php?curid=7077266>.<sup>26</sup>

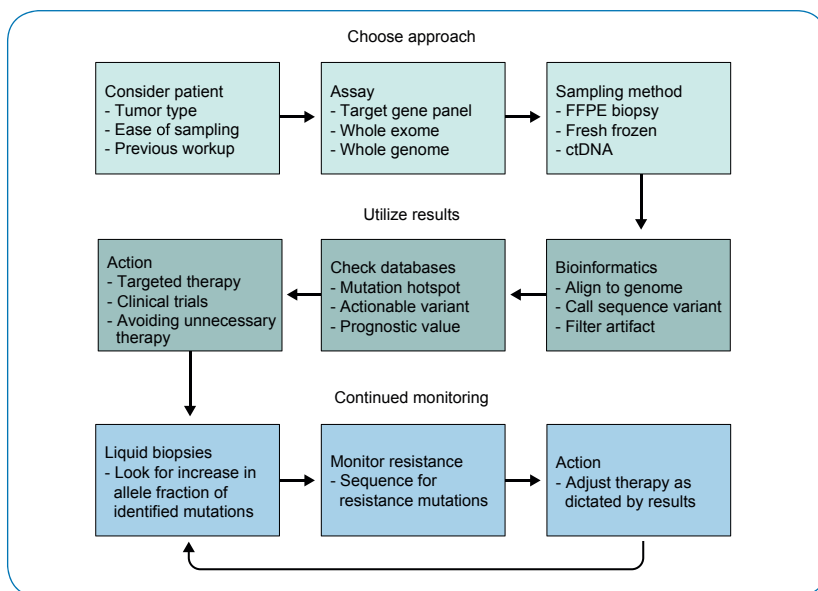


Figure 5. Suggested workflow for oncologists using Next-Generation Sequencing (NGS) for patient care. Reprinted from Gagan J, Van Allen EM. *Genome Med*. 2015;7(1):80. Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>).<sup>7</sup>

## Key Fact No. 2

### What is circulating tumor DNA (ctDNA)?

ctDNA are fragments of DNA that are released into the blood from apoptotic tumor cells.<sup>7</sup> Sequencing of the ctDNA is a recent innovation for monitoring clinically relevant molecular changes that may be driving disease progression and treatment resistance.<sup>24</sup> As a minimally invasive alternative to tissue biopsy, assays are now available (with additional assays in development) that apply the high sensitivity and specificity of NGS to the detection of cancer from a simple blood draw (ie, a “liquid biopsy”) (see **Figure 6**). This advance is particularly important to the estimated 20% of patients who undergo a successful biopsy but who are unable to yield enough tissue to perform molecular analysis. ctDNA may also have utility in the detection of minimal residual disease and may help improve diagnostics and prognostication.<sup>7,24</sup>

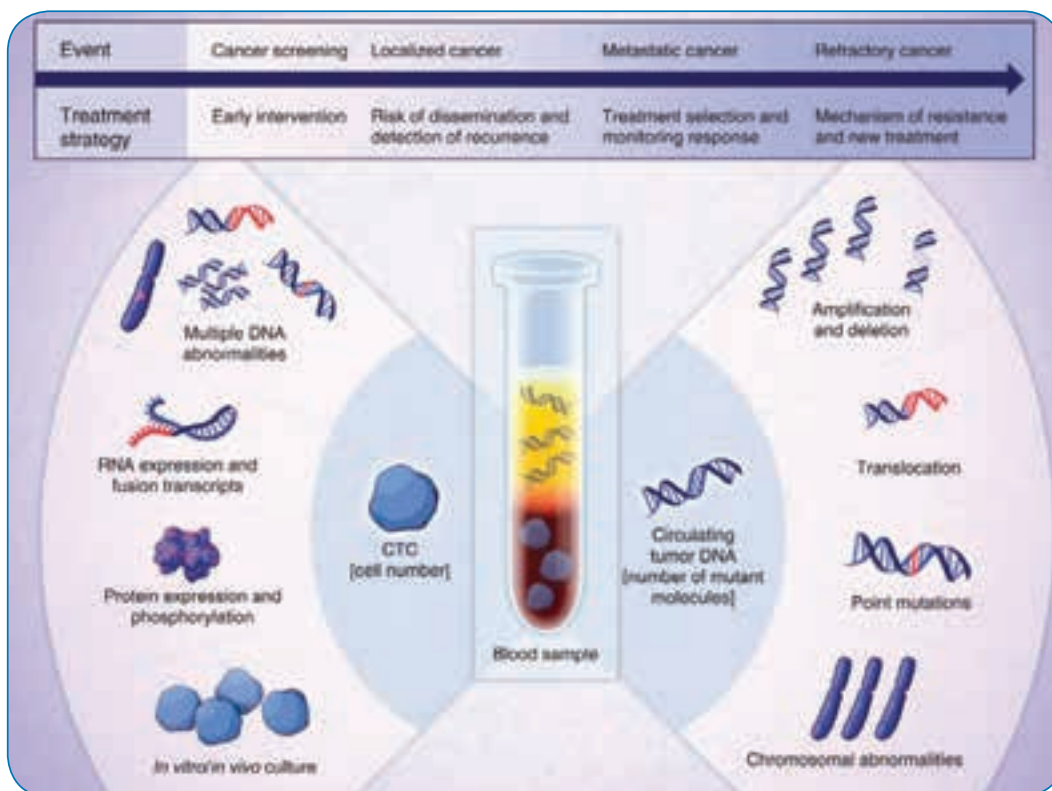


Figure 6. Application of liquid biopsy. Reprinted from Harber DA, Velculescu VE. *Cancer Discov.* 2014;4(6):650-61, with permission from the American Association for Cancer Research.<sup>28</sup>

## Neoantigens in immunotherapy

When tumor-specific DNA mutations alter the function of proteins, cancer cells acquire antigens on their surface that are absent from the normal genome (neoantigens).<sup>29</sup> These neoantigens are identified by sequencing the exome—the coding regions of DNA—and expressed genes or RNA from tumor cells.<sup>29,30</sup> Neoantigen selection is facilitated by computer (in silico) prediction models. It is believed that tumors known to be highly mutated are more likely to be populated with neoantigens, which may make them targetable by active immune cells.<sup>30</sup> Small sets of selected neoantigens can then be used for vaccine development or cell transfer (see **Figure 7**). NGS is enabling researchers to characterize the total number of tumor-specific antigens present in a tumor—the tumor mutational burden (TMB)—in multiple tumor types.<sup>29,30</sup> In lung cancer, for example, smoking is a disease risk factor due to its ability to cause DNA mutations that substantially increase TMB.<sup>31</sup> In a recent study, a higher TMB was shown to be predictive of more durable clinical benefits, such as in patients with NSCLC who have been treated with programmed death receptor 1 (PD-1) inhibitors.<sup>32</sup>

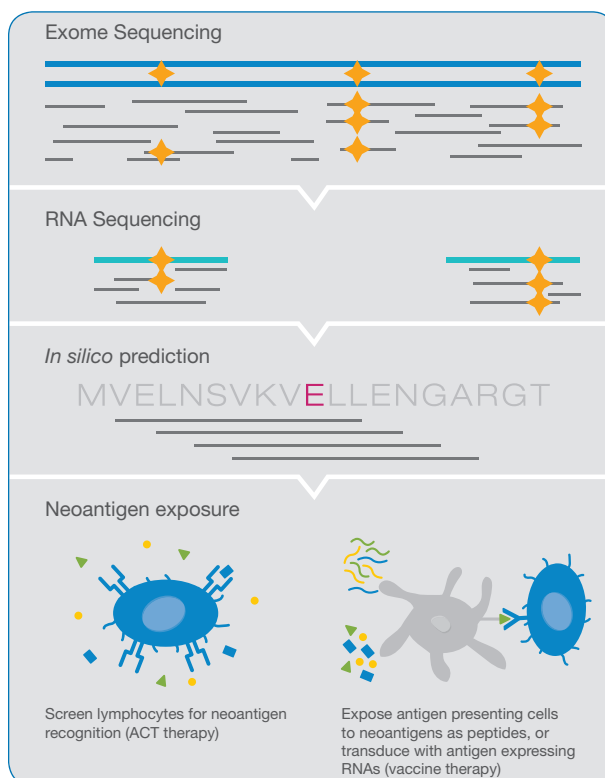


Figure 7. Sequencing is essential for development of personalized immunotherapies. Image by Illumina, Inc. 2016.<sup>33</sup>

## Cancer pharmacogenomics

Pharmacogenomics explores how genetic variants can affect drug efficacy and toxicity. Inherited (or, germline) mutations can affect the pharmacokinetics and pharmacodynamics of a selected treatment, which may in turn impact a patient’s response to that treatment. Therefore, the DNA sequence of certain genes can help determine the amount of drug to be prescribed or what adverse events might be anticipated in certain phenotypes.<sup>4</sup> Multiple factors can contribute to variations in drug response, including environmental and genetic factors (see **Figure 8**).<sup>34</sup> NGS can be used to sequence a targeted subset of genes with the aim of selecting treatments that may help reduce toxicity and cost, and improve patient outcomes.<sup>22</sup>

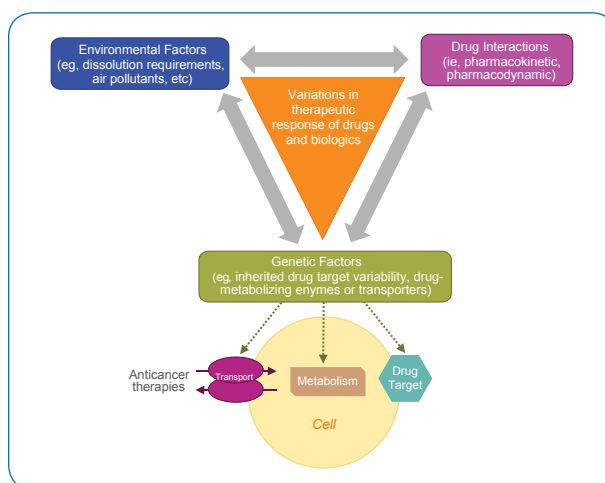


Figure 8. Factors contributing to drug response. Figure adapted from Lee W, et al. Cancer pharmacogenomics: powerful tools in cancer chemotherapy and drug development. *Oncologist*. 2005;10(2):104-111.<sup>34</sup>

# Clinical trial designs incorporating NGS

## Key Fact No. 3

NGS biomarker panels are now being used as selection criteria for participation in clinical trials evaluating the efficacy and safety of targeted therapies. Two examples of these new types of clinical trials are *umbrella* and *basket* trials.<sup>35</sup>

**Umbrella trials** are designed to evaluate a single cancer type or histology using a variety of drugs targeting different mutations—in essence, the “molecular portrait” of a tumor: 1 disease, several molecular subtypes, several therapies (see **Figure 9**).<sup>35,36</sup> Umbrella trials can test whether one or more precision approaches for managing a traditional diagnosis (for example, lung adenocarcinoma) might lead to better outcomes than the current standard of care.<sup>7,36</sup> An example of an umbrella trial is the BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial in patients with NSCLC. In this novel personalized medicine trial, tumors were prospectively biopsied and analyzed for biomarkers (such as *EGFR*, *ALK*, *ROS1*, and others). Patients were then randomized to receive the targeted treatment determined to have the best potential for enabling positive outcomes.<sup>37</sup>



Figure 9. Umbrella trials. In umbrella trials, multiple targeted agents are tested against multiple genetic mutations within the same cancer. Reprinted from American Association for Cancer Research. AACR Cancer Progress Report 2015. *Clin Cancer Res.* 2015;21(suppl 1):SI-S128. [http://cancerprogressreport.org/2015/Documents/AACR\\_CPR2015.pdf](http://cancerprogressreport.org/2015/Documents/AACR_CPR2015.pdf).<sup>38</sup>

**Basket trials** evaluate patients who are assigned a targeted treatment based only on the genetic abnormality identified, irrespective of the type of cancer present (see **Figure 10**).<sup>7,37</sup> In other words, each tumor type is grouped into a single cohort so that the treatment’s efficacy and safety can be assessed in all patients. Basket trials have the added benefit of being able to include rare cancers that otherwise cannot be studied in randomized controlled trials.<sup>36,37</sup> Basket trials can include 1 drug and several tumor types; 1 drug and 1 molecular alteration in several tumor types; or 1 drug with several molecular alterations and several tumor types.<sup>36</sup> An example of a basket trial is the National Cancer Institute–Molecular Analysis for Therapy Choice (NCI-MATCH) trial. In this basket trial, patients with lymphoma and advanced solid tumors—gastrointestinal stromal tumors, NSCLC, breast, gastric, melanoma, and thyroid—are being evaluated for treatment with a targeted drug combination to determine whether targeted therapy is superior to standard therapies.<sup>37</sup>



Figure 10. Basket trials. In basket trials, a targeted agent against a specific mutation (green dot) is explored across multiple cancers. Reprinted from American Association for Cancer Research. AACR Cancer Progress Report 2015. *Clin Cancer Res.* 2015;21(suppl 1):SI-S128. [http://cancerprogressreport.org/2015/Documents/AACR\\_CPR2015.pdf](http://cancerprogressreport.org/2015/Documents/AACR_CPR2015.pdf).<sup>38</sup>



## **Next-Generation Sequencing: Revolutionizing Patient Care in Your Oncology Practice**

The landscape of oncology clinical practice is on the verge of a revolution in patient care. For the numerous types of cancer, NGS can offer the ability to simultaneously screen for multiple gene variants. Using just a very small amount of sample, NGS high-throughput technology analyzes millions of fragments of DNA in parallel with high efficiency, low costs, and short processing times. NGS is helping to improve cancer diagnostics, prognosis, selection of a more precise and personalized treatment plan, and more accurate treatment adjustments when needed.<sup>22,39</sup>

To learn more about integrating Next-Generation Sequencing into your clinical practice, visit [www.illumina.com/oncology](http://www.illumina.com/oncology)

### **Additional Resources**

- Genetic Testing Registry: <https://www.ncbi.nlm.nih.gov/gtr/>
- The PharmGkb: <https://www.pharmgkb.org/>
- FDA Table of Genomic Biomarkers in Drug Labeling: <https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>

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