CARIS LIFE SCIENCES

Whole Exome and Whole Transcriptome Sequencing in Oncology

Improving Patient Outcomes and Reducing Costs

January 2024

Key Learnings

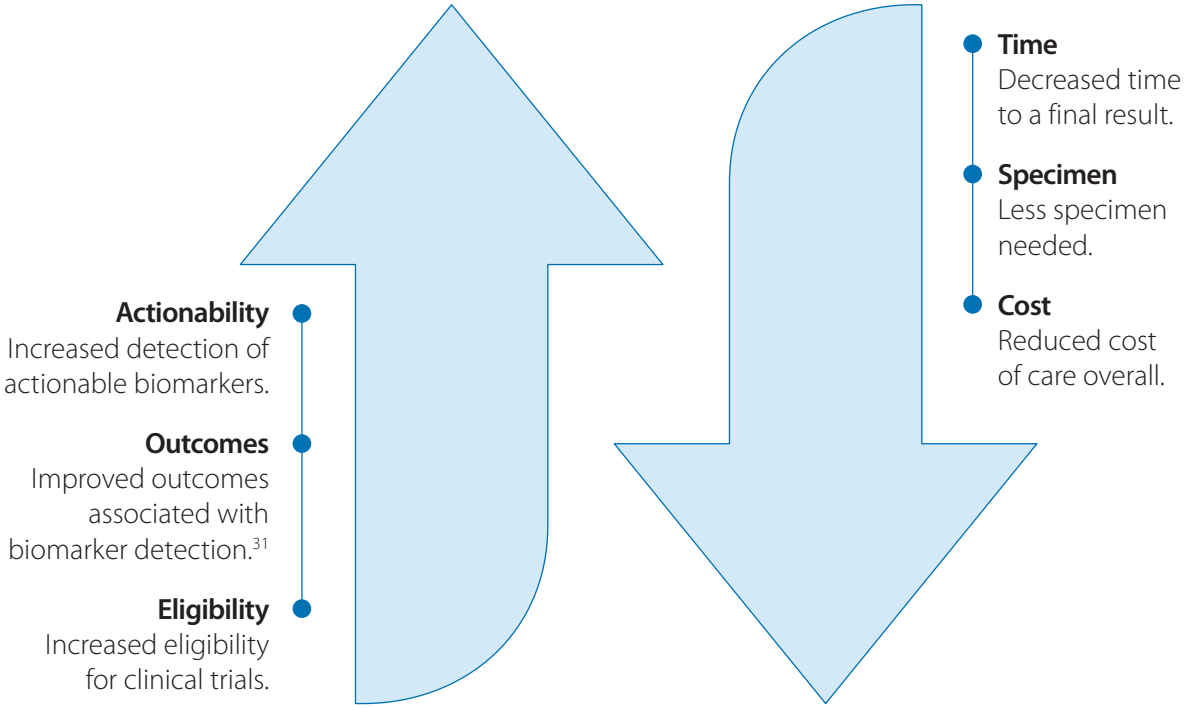
Oncology care is transitioning from universal to personalized treatment, also known as **precision oncology**.

Precision oncology relies on the detection of molecular **biomarkers** to inform selection of the optimal therapy for an individual patient.

Since 2020, the number of biomarker-associated **targeted therapies** approved for use in cancer has grown rapidly.

Whole exome and whole transcriptome sequencing of DNA and RNA offers the most in-depth insights into a patient's cancer biomarkers.

Compared to sequential single gene or small panel testing, **whole exome and whole transcriptome sequencing offers:**



Executive Summary

Cancer affects nearly 2 million Americans each year, with more than 600,000 deaths per year.[3] Despite billions of dollars in annual funding from the National Institutes of Health (NIH) and National Cancer Institute (NCI), the complexity of this broad disease remains a major challenge in healthcare. The annual burden of cancer care in the United States was more than $200 billion in 2020,[4] or $100,000 per patient, and is expected to increase over the coming decades. Better tools are needed to detect and treat cancer earlier and more effectively to improve lives while managing healthcare costs.

2,000,000
Americans per year

$200,000,000 burden
$100,000 per patient

The medical community's understanding of cancer has advanced rapidly in the 21st century, largely due to innovations in genomic sequencing and computing power revealing deep insights into the cellular pathways and molecular nature of all types of cancer. Next-generation sequencing (NGS) has far surpassed earlier techniques as a way to analyze tumors. By combining massively parallel genomic processing with big data bioinformatics, NGS has made precision oncology a reality for today's clinicians and patients, providing molecular tools that guide therapy decisions and improve patients' lives.

Cancer treatments have likewise experienced a major shift. While surgery was once the only option, today a range of therapies are available, from radiation and hormone therapy to chemotherapy, immunotherapy, and targeted or biomarker-associated drugs. The drug discovery and development processes are also evolving, from hypothesis-driven, high-throughput searches for blockbuster drugs to big data-guided identification of biomarker-associated "niche-buster" drugs for well-defined patient cohorts.

To navigate this explosion in targeted therapies and maximize cost-effective patient care, the healthcare ecosystem must embrace molecular profiling as standard of care. Whole exome sequencing (WES) and whole transcriptome sequencing (WTS), in particular, simplify and streamline the clinical decision-making process, empowering clinicians to develop the most informed care plans for their patients. American Society of Clinical Oncology (ASCO) guidelines recommend that patients with advanced and metastatic solid tumors undergo molecular profiling when there are approved biomarker-linked therapies and support the rationale for testing all solid tumors based on site-agnostic drug approvals.[5]

Biomarkers: Doorways into Precision Oncology

Biomarkers may be used as diagnostic indicators of the presence or type of cancer, as predictive markers for patients likely to benefit from certain treatments, as prognostic indicators for the likely patient outcome, or as tools to monitor therapy response, residual disease, or recurrence.

Analyzing key molecular features at the DNA or RNA level helps identify the errors and cellular dysfunction that define a specific cancer. Comprehensive approaches such as WES also detect genome-wide molecular signatures that single-gene or small panel testing alone cannot fully reveal.

A wide array of molecular diagnostic and prognostic tools have emerged over the past few decades, ranging from single-gene and small panel testing to WES analysis of all 23,000+ protein-coding genes. Early advantages existed for single gene tests and small hotspot panels, mostly in cost savings and specimen preservation. However, major improvements in molecular science, sequencing technology, and computing power have converged to enable WES/WTS to be delivered in a timely, cost effective manner relative to these less comprehensive tests.

What is precision oncology?

- Precision oncology is the use of molecular profiling – including analysis of DNA and RNA – to identify a cancer's targetable alterations.
- These molecular insights enable the tailoring of therapy to patients likely to benefit, while sparing exposure, toxicity, and cost for those who will not.
- The goal of precision oncology is to deliver the right therapy to the right patient at the right dose and time.[2]

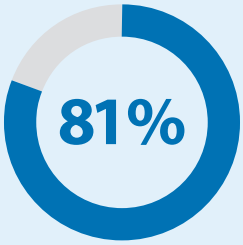
What is a comprehensive molecular profiling approach?

A comprehensive molecular profiling approach analyzes DNA (by WES) and RNA (by WTS) to generate the most in-depth picture of a patient's cancer.

WES/WTS Offers a More Comprehensive Picture from the Start

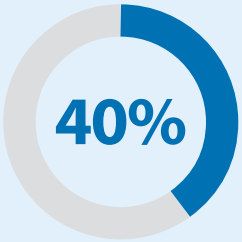
- **Improving Patient Outcomes** – WES/WTS enables clinicians to obtain a wealth of genome-wide biomarker data in one go, enhancing the likelihood of matching patients with targeted therapies and thus helping improve outcomes.[31] Less comprehensive or accurate tests can miss biomarkers that may identify therapeutic options, meaning that patients may receive less beneficial therapies.
- **Time Savings** – Compared to running multiple, sequential multigene panels to reach an actionable result, a single WES/WTS run takes less time and provides results earlier in the patient journey.
- **Specimen Preservation** – WES/WTS derives the maximum data from a single patient sample, thereby minimizing the need for additional biopsies. Sequential multigene panels, on the other hand, rapidly exhaust tumor samples and may require multiple biopsies.
- **Cost Management** – When small panels fail to detect actionable biomarkers, additional testing cumulatively costs more than the initial outlay for a single WES/WTS assay while delaying treatment decisions and likely increasing the downstream cost of care.
- **Value Across the Healthcare Ecosystem** - Insights from WES/WTS empower clinicians to make the most informed choices for their patients and help payors to reduce waste and harm from insufficient molecular profiling and the resultant suboptimal therapy selections.

Comprehensive profiling reduces the likelihood of missing genetic alterations



of alterations are missed by small hotspot panels.[6]

Comprehensive profiling reduces the likelihood of missing targeted therapy options



of patients tested with non-NGS methods had a missed targeted therapy option versus 3% of patients who underwent comprehensive genomic profiling (CGP).[7]

Comprehensive profiling reduces the overall cost of treatment

in overall total cost of care due to more optimal treatment in patients with lung cancer who received broad versus narrow panel testing.[8]

Conclusions

Despite strong clinical guidelines supporting broad biomarker testing, patients are currently under-profiled for biomarkers with FDA-approved therapies. A comprehensive profiling approach enables oncologists to select the right therapy from the start while avoiding costly non-beneficial therapies. Such therapy optimization early in the patient journey helps improve patient outcomes while minimizing downstream costs, ineffective therapies, and unnecessary toxicity.

Improving reimbursement consistency will help clinicians to integrate WES/WTS into their oncology practices, ultimately improving the lives of cancer patients while better managing healthcare costs.

Introduction

Oncology is evolving at an unprecedented rate. While the 20th century was a period of great therapeutic innovation, during which chemotherapy, hormone therapy, and immunotherapy emerged as treatment mainstays, the 21st century has started on an even more impressive trajectory. Its first quarter has been characterized by a staggering growth in genomic sequencing and targeted therapies, heralding a new era of precision, or personalized, oncology.

Precision oncology is enabled by molecular profiling, which provides the information needed to leverage biomarker-driven targeted therapies and maximize patient outcomes. The most informative type of profiling is a comprehensive approach, combining analysis of the entire exome (DNA) and transcriptome (RNA) through WES/WTS to deliver detailed molecular insights. These insights enable better clinical care, increased access to clinical trials, and innovative research. Most importantly, WES/WTS can provide greater clinical and economic value than traditional panel testing approaches.

In this review, we explore the role of whole exome sequencing (WES) and whole transcriptome sequencing (WTS) in biomarker analysis, their advantages over other testing options, and their impact on personalized cancer care, including why WES and WTS are critical to healthcare management.

From Scalpels to Genomes: The Changing Landscape of Cancer Care

The oncology paradigm began transitioning from surgery-dominated to molecularly informed in the second half of the 20th century **(Figure 1)**. Until the birth of chemotherapy in the 1940s, the oncology field relied on radical surgical methods to remove tumors before they spread. As understanding of cancer on a cellular level increased, chemotherapy gained popularity and was combined with surgery and radiation to improve patient outcomes further. Over the subsequent decades, more targeted treatments, including hormone therapies and immunotherapies, emerged along with significant advances in cancer genetics.

The first quarter of the 21st century has seen a significant shift in how oncology is practiced, driven by a rapid acceleration in nucleic acid sequencing technology. Traditionally, all patients with the 'same' cancer type (as defined by clinical and histological features) were treated using the same therapeutic regimen, typically involving surgery, chemotherapy, and hormone therapy. These standard treatments improved outcomes in some patients but were less effective in others. Advances in sequencing technology vastly expanded our knowledge of cancer on a molecular level. These insights helped explain why one-size-fits-all therapies can elicit different responses in different patients, accelerating the arrival of the precision oncology era.

Recent studies have shown how unique each tumor is on a molecular level,[6] so it follows that treating them optimally would require individualized therapies. The oncology field has, therefore, started to move from broad to more precise oncology treatments tailored to a tumor's molecular makeup. The pace of this transition accelerated rapidly in the 2010s amid significant growth in the number of approved biomarker-targeted therapies and appears likely to increase exponentially over the coming years.

Milestones in Cancer Therapy (1900–2023)

1900-1924	1925-1949	1950-1974	1975-1999	2000-2023
				SURGERY
			RADIATION THERAPY	RADIATION THERAPY
			CHEMOTHERAPY	CHEMOTHERAPY
			HORMONE THERAPY	HORMONE THERAPY
			IMMUNOTHERAPY	IMMUNOTHERAPY
			TARGETED THERAPY	TARGETED THERAPY
1902 – Boveri suggests cancer arises from chromosomally damaged, rapidly dividing single cells. **1909** – Ehrlich proposes the immune system normally suppresses tumor formation. **1911** – Rous shows cancers can be caused by viruses.	**1941** – Huggins shows that hormone therapy can cause prostate tumors to regress. **1942** – Nitrogen mustard used as the first chemotherapeutic agent to treat cancer. **1949** - FDA approves nitrogen mustard for cancer.	**1950s** - Other alkylating agents and antimetabolites are adopted as therapies. **1958** – Combination chemotherapy shown to improve outcomes. **1973** – Tamoxifen approved in UK.	**1977** – FDA approves tamoxifen, the first hormone therapy drug. **1979** - TP53 discovered. **1984** - Her2 (neu) identified. **1994/5** - BRCA1/2 cloned. **1998** – FDA approves the first biomarker-targeted therapy, trastuzumab.	**2000** – FDA approves first antibody-drug conjugate, gemtuzumab ozogamicin. **2004** – First anti-angiogenesis agent, bevacizumab, approved. **2011** – First checkpoint inhibitor, ipilimumab, approved. **2017** – First CAR T-cell therapy, tisagenlecleucel, approved.

CHEMOTHERAPY

Interferes with the cell cycle to interrupt division and kill cells, particularly rapidly dividing tumor cells.

HORMONE THERAPY

Lowers hormone levels or activity to treat hormone-driven cancers, such as breast and prostate cancer.

IMMUNOTHERAPY

Boosts response or provides components (e.g., checkpoint inhibitors) to help immune system kill cancer cells.

TARGETED THERAPY

Affects cancer-specific cellular processes to accelerate tumor cell death while leaving normal cells intact.

Figure 1. The evolution of cancer therapy in the 20th and early 21st centuries.[60-62] The 20th century was a period of great innovation in oncology, commencing with Boveri's 1902 suggestion that cancer arises from chromosomally damaged, rapidly dividing single cells[9] and closing with the FDA's 1998 approval of the targeted breast cancer therapy trastuzumab. With an explosion in approvals for biomarker-targeted therapies, the 21st century promises to be even more revolutionary.

Biomarkers Guide the Way to Targeted Therapies

In precision oncology, clinicians leverage information on detectable or measurable biological characteristics called biomarkers to inform treatment decisions. Biomarkers can be classified into three categories based on their relationship to the associated drug **(Figure 2)** and further characterized as diagnostic, predictive, or prognostic, depending on the information they provide **(Figure 3)**. Diagnostic biomarkers can indicate the presence, type, or stage of cancer. Information derived from predictive biomarkers can help guide therapy selection, enabling oncologists to employ the drug most likely to benefit their patients while avoiding the toxic side effects of unhelpful therapies. Biomarker data can also provide critical prognostic information. Examples of oncology biomarkers include genomic alterations, RNA transcript variations, proteins, and multigene or chromosomal signatures.

Biomarker-associated therapies now dominate FDA approvals in oncology. For example, nine of the ten new breast cancer drugs approved by the FDA between 2009 and 2018 were targeted therapies based on specific biomarkers.[10] Furthermore, in 2020, the FDA approved a total of 28 targeted therapies for use in patients with specific molecular biomarkers.[5]

Biomarkers can be detected and measured through molecular profiling, including genomic profiling of genes (DNA) or transcripts (RNA) to assess phenotype or function **(Figure 4**).

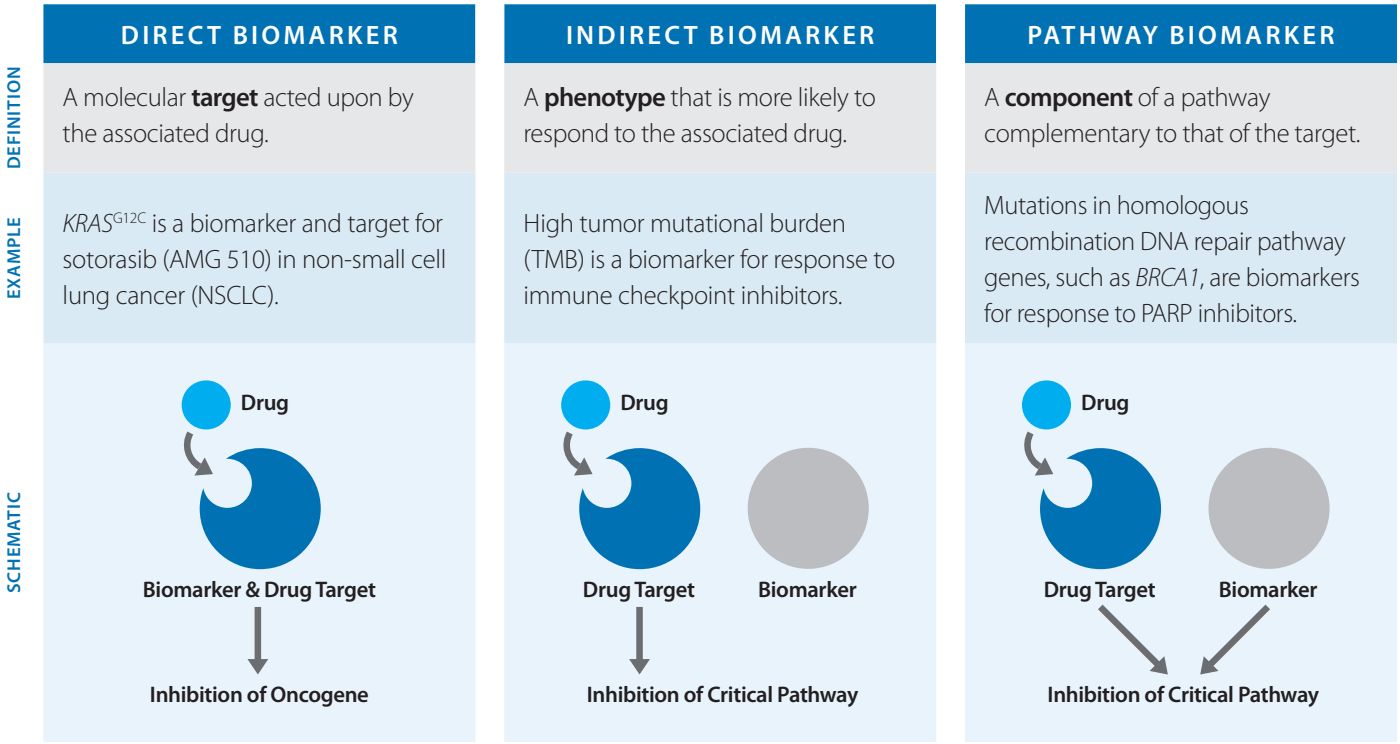


Figure 2. Biomarkers can be classified based on their relationship to the associated drug. Examples are provided for each category of biomarkers.

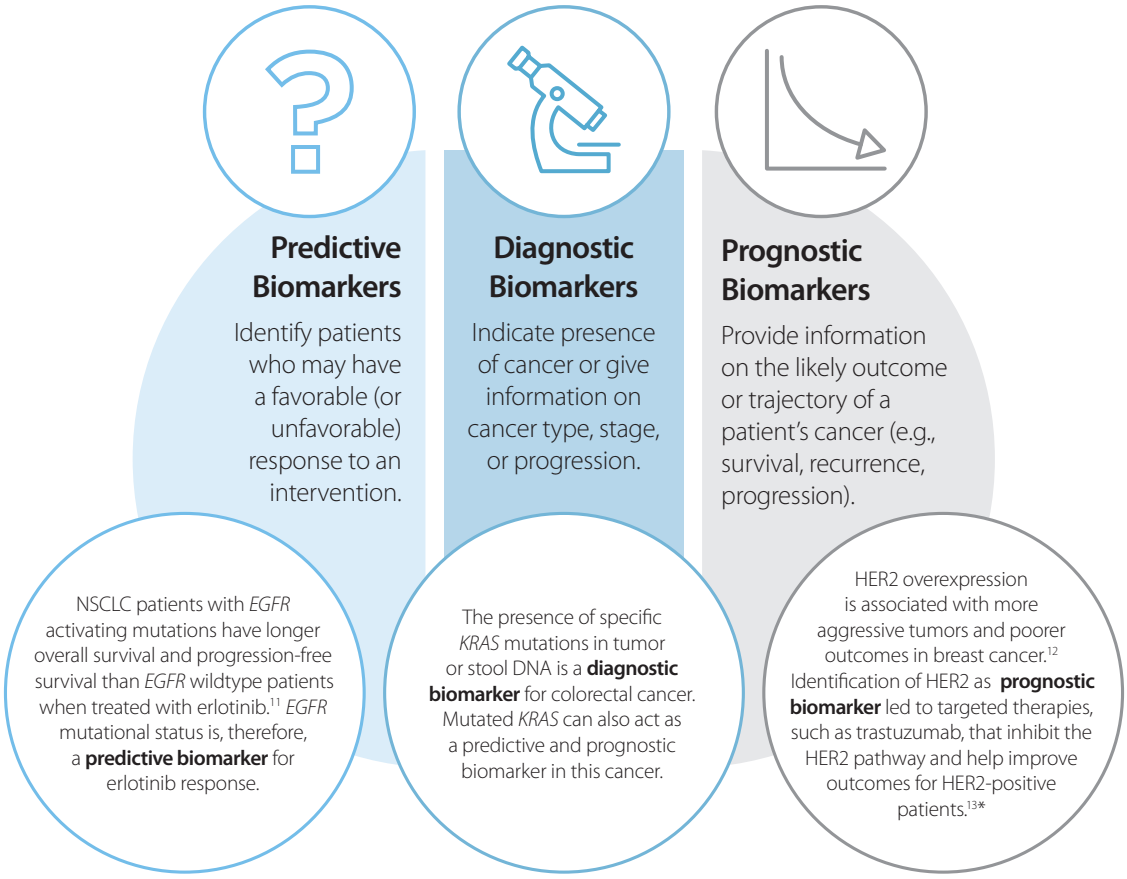


Figure 3. Biomarkers can be also classified based on the information they provide. Examples are provided for each biomarker category.

Profiling is the Key to Decoding Cancer's Molecular Blueprint

DNA

Mutations and copy number alterations (variations) can be detected using the polymerase chain reaction (PCR) or sequencing, typically next-generation sequencing (NGS), while DNA methylation is analyzed using pyrosequencing or PCR. DNA sequencing can be performed for an entire gene or, as in the case of hotspot panels, within specific regions containing common cancer-associated alterations. NGS-based multigene panels are FDA-approved for several tumor types. These targeted panels identify known alterations in key cancer genes but do not provide a comprehensive overview of a tumor's molecular makeup.

Identifying all genomic or coding alterations requires whole genome sequencing (WGS) or whole exome sequencing (WES). Whereas WGS offers information on the entire genome, including non-coding regions, WES generates data from just the ~23,000 genes encoding functional proteins. These genes comprise only ~2% of the entire genome but disproportionately represent the underlying molecular cause of most cancers and are logically the focus of diagnosis and intervention. WES, therefore, provides a more focused analysis than WGS without the loss of clinically actionable data.

RNA

RNA, which is transcribed from DNA, can better represent which genes are actively involved in cancer. While mutations detected in DNA may be silent (not expressed) and therefore of little clinical relevance, those in RNA are one step closer to producing an abnormal protein. RNA is also needed to learn about gene expression and splice variants through *in situ* hybridization and RNA sequencing. RNA sequencing provides information that DNA cannot and is superior for detecting expressed fusions.[14-16]

As with DNA, RNA sequencing can be performed for one, multiple, or all transcribed genes, in either targeted areas or the full coding region. Whole transcriptome sequencing (WTS) uses NGS to analyze all (potentially 23,000) transcribed genes in full and generate information on splice variants and gene fusions, including fusions not previously described. This information can help define molecular signatures, stratify risk, and guide targeted therapy use. In combination with WES, WTS provides information on all expressed genes, thereby detecting alterations associated with FDA-approved therapies, standard-of-care treatments, and investigational therapies in clinical trials.

Molecular Signatures

In addition to individual gene alterations, profiling can provide information on specific patterns or combinations of molecular features. These molecular signatures may be associated with particular cancer types, prognoses, or therapeutic responses. Examples of molecular signatures include:

- Genomic loss of heterozygosity (gLOH): Loss of one copy of a genomic region, known as gLOH, may cause tumor suppressor gene inactivation, thereby promoting cancer development. gLOH is indicative of a form of defective DNA repair called homologous recombination deficiency. When a tumor exhibits DNA repair mechanism impairment, drugs targeting a secondary repair pathway can kill tumor cells without harming normal cells, a phenomenon called synthetic lethality. Thus, gLOH is a biomarker for therapeutic response to PARP inhibitors which target the single-strand break DNA repair pathway.[17]
- Homologous recombination deficiency (HRD): Related to gLOH, inefficient repair of damaged DNA via homologous recombination can contribute to the development of cancer. HRD often results from aberrations in key DNA repair genes, including *BRCA1/2, ATM, PALB2,* and *CHEK2*, and is associated with increased sensitivity to PARP inhibitors, as above.[17,18]
- Microsatellite instability (MSI): Defective mismatch repair (dMMR) caused by alterations in mismatch repair genes is associated with hypermutability of microsatellite loci. MSI analysis can identify candidates for immunotherapy[19] or MSI-indicated clinical trials and diagnose Lynch Syndrome in colon and endometrial cancers.
- Tumor mutational burden (TMB): High TMB, a measurement of the number of somatic mutations per megabase of DNA sequenced, is an indication for treatment with pembrolizumab.[20] WES is the gold standard for measuring TMB as it covers the entire coding region of the genome.[5] Measurements derived from multigene panels or comprehensive genomic profiling, on the other hand, vary significantly from panel to panel owing to variable and incomplete coverage.

Types of Molecular Profiling

Small Panel Testing (<50 Genes)	Large Panel Testing (>50 Genes)	Whole Exome Sequencing/ Whole Transcriptome Sequencing
DNA or RNA analysis of a small set of cancer-associated genes by sequencing entire genes or within specific regions of genes by hotspot testing.	DNA or RNA analysis of a broader set of cancer-associated genes (up to several hundred genes) by sequencing entire genes or within specific regions of genes by hotspot testing.	In-depth genomic analysis of DNA and RNA to identify multiple molecular features, including alterations, expression, and signatures.

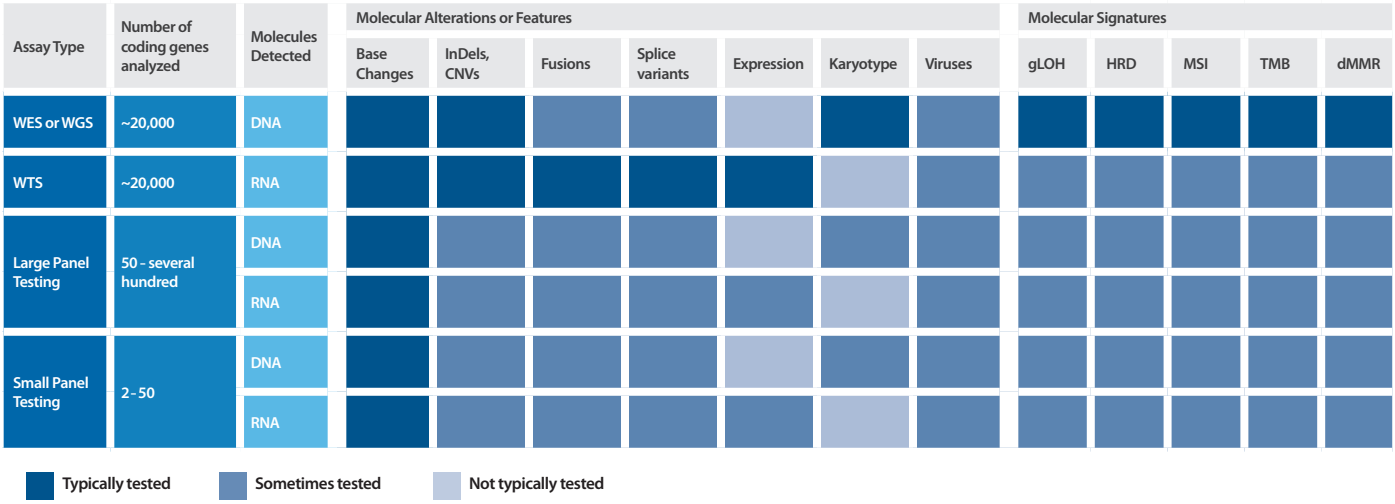


Figure 4. Oncology molecular profiling tests range in complexity and the level of information they provide. The main types of genomic testing employed in cancer care are shown above. These tests range from the analysis of a specific change in a single gene to profiling of the entire exome or genome. More complex methods, such as WES and WTS, provide information not only on single molecular alterations but also on genome-wide molecular signatures.

Is Bigger Better? Multigene Panels vs. WES/WTS

Choosing the most appropriate genomic profiling approach for an individual patient relies on a variety of factors. Below, we examine the advantages and limitations of several approaches.

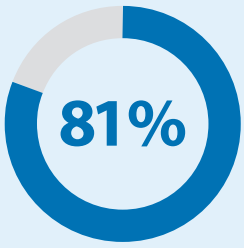
Multigene Panels

Multigene panels may include a small or large number of genes. Small multigene panels that fail to detect pathogenic alterations typically necessitate subsequent testing by additional small panels. Large multigene panels that test for all actionable alterations, including those associated with an approved tumor type-agnostic therapy (i.e., MSI-H, TMB, and specific fusions), are more resource-efficient than such serial testing for individual biomarkers.[5]

Small Multigene Panels

Small panels (2-50 genes) typically have a faster turnaround time, lower cost, increased reimbursement, and decreased specimen requirement compared with larger panels. Furthermore, hotspot panels, which analyze a specific set of common actionable pathogenic alterations, typically provide information immediately applicable to therapy selection, with little time needed for data analysis or result interpretation.

However, because small panels only test for a small portion of all cancer-associated genomic alterations, they can miss critical clinically actionable information. In a study of more than 10,000 cancer patients, 81% of the mutations detected by CGP fell outside of the targeted regions of commercially available hotspot panels.[6] This information deficit can lead to suboptimal treatment decisions or the need for further testing, requiring increased tissue, time, and expense.



of alterations detected by comprehensive profiling are missed by hotspot panels.[6]

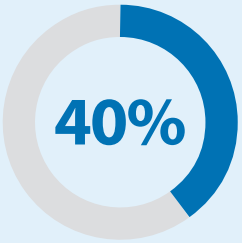
Large Multigene Panels

Large (>50 genes) NGS-based panels reduce the likelihood of missing targeted therapy options compared to smaller, non-NGS panels. In a study of patients with newly diagnosed advanced NSCLC (aNSCLC), unsuccessful genotyping occurred in 52% of patients tested with non-NGS methods compared with only 13% of NGS-tested patients.[7] Four in ten patients receiving non-NGS testing had a potentially missed targeted therapy, compared with only one in ten NGS-tested patients. Furthermore, NGS testing increases the ability to identify and rule out potential targeted therapies and may also help increase testing for more recently approved biomarkers.[7]

Even when small panels are NGS-based, they are still outperformed by larger NGS panels as increasing panel size increases the number of actionable biomarkers identified. In a study of refractory cancer patients profiled using a small (46- or 50-gene) hotspot NGS panel and a larger (409-gene) whole exome-based NGS panel, four out of ten had at least one actionable alteration missed by the smaller panel but detected by the larger panel.[23] One in five of these patients was subsequently treated with a biomarker-matched therapy indicated by the large panel and had significantly improved overall survival compared with patients who received unmatched therapy. This study, which used a panel incorporating genes not included in current clinical guidelines, demonstrates that larger panels can identify more patients eligible for targeted therapies and help improve outcomes. However, even these larger panels are unlikely to pick up rare and novel cancer-associated alterations or more complex molecular features and signatures. Once again, missed findings may result in the need for further testing to identify an appropriate therapy.

"Comprehensive" Genomic Profiling (CGP)

Compared to other panel-based NGS tests, CGP reduces the likelihood of missing targeted therapy options. In a study of newly diagnosed aNSCLC patients, unsuccessful genotyping occurred in only 5% of patients tested using CGP, compared with 13% of patients tested using other NGS tests.[7] Targeted therapies were potentially missed in 3% and identified in 30% of CGP-tested patients compared with 13% and 28% of patients tested with other NGS tests. CGP also has negative predictive value, ruling out targeted therapy in 67% of patients, compared with 59% of standard NGS-tested patients. However, in current usage, the term "comprehensive" can be misleading as it is typically used to describe the analysis of hundreds of DNA genes, and not analysis of all 23,000 protein-coding genes in both DNA and RNA.



of patients tested with non-NGS methods had a missed targeted therapy, versus 3% of patients who underwent CGP.[7]

WES and WTS

Adherence to National Comprehensive Cancer Network (NCCN) cancer diagnosis guidelines requires testing for multiple biomarkers using multiple technologies.[24] WES in combination with WTS offers a truly comprehensive approach to profiling and provides maximum insights from the start, without the need for additional downstream testing. WES/WTS generates the most complete blueprint of a patient's cancer and empowers clinicians to meet their needs.

WES and WTS generate information on all the protein-coding genes (~23,000 in total) in the genome using an amount of tissue similar to multigene panels. Furthermore, a single WES or WTS run can deliver more information using less tissue in less time and at a lower cost than multiple DNA or RNA panels run sequentially. WES and WTS can also identify variants not picked up by targeted DNA and RNA sequencing panels to inform care decisions for patients whose standard therapies have failed. In addition to identifying mutations, copy number alterations, and other genomic alterations, WES/WTS also typically reports on a range of cancer-associated aberrations, measurements, and molecular signatures, including gLOH, HRD, MSI, and TMB.

A single WES or WTS run can deliver more information using less tissue in less time and at a lower cost than multiple DNA or RNA panels run sequentially.

WES/WTS can also inform on acquired resistance to treatments and suggest potential synergistic therapy combinations,[25] as well as providing substantial clinical benefit to patients with cancer of unknown origin or rare cancers.[26] Additionally, by taking a tumor-agnostic approach versus using tumor-specific panels, WES/WTS can detect biomarkers that have targeted therapies in other cancer types, indicating the potential to apply those drugs more broadly.[27] Armed with these molecular insights, clinicians can identify the most suitable therapies and trials available to their patients today. Having a full molecular blueprint *in silico* also facilitates future use of newly approved biomarkers and therapies, i.e., "futureproofing."

Aside from its clinical benefits, WES/WTS is also a powerful research tool for identifying new predictive biomarkers.[28] Pancreatic ductal carcinoma has the worst prognosis among common cancers – a situation compounded by a scarcity of predictive biomarkers and therapeutic targets. In a recent study, a comprehensive profiling approach involving WES and RNA sequencing was used to identify novel potential markers and targets for this cancer.[29]

How Does WES/WTS Stack Up?

Overall, WES/WTS provides the most efficient and cost-effective way to obtain the maximum information on a patient's cancer simultaneously, potentially identifying rare mutations and expanding treatment options **(Table 1)**. WES/WTS is a "one and done" approach. Small, multigene panels, on the other hand, focus on a specific set of cancer-associated genes and often, as with hotspot panels, only within the most frequently mutated regions of those genes. This sequential approach may seem more cost-effective but often misses clinically relevant information. If initial panel testing is uninformative, additional biopsies and further tests may be required, leading to delays in treatment and increased costs compared to WES/WTS.

SEQUENTIAL MULTIGENE PANELS	WES/WTS
Less information Multigene panels analyze specific genes, meaning that alterations outside of these genes are missed.	**More information** WES/WTS analyze all known ~23,000 coding genes, resulting in unbiased detection of all alterations.
Slower time to actionable results Compared to WES/WTS, total run time is longer when multiple sequential panels are needed to reach an actionable result.	**Faster time to actionable results** A WES/WTS run takes a comparable time to a single panel but offers a complete blueprint from the start.
Increased sample requirement Each sequential panel requires additional tissue. Tumor samples can become exhausted, necessitating further biopsy or cessation of testing.	**Smaller sample requirement** WES/WTS uses a similar amount of tissue to a single panel and less overall material than multiple sequential panels.
Increased cost Although panels are individually cheaper than WES/WTS, cost adds up when running multiple panels.	**Decreased cost** Compared to running multiple panels, a single WES/WTS run comes at a similar cost and avoids unnecessary downstream costs.
Increased administrative burden Each panel requires ordering, financing, and reporting. Running multiple panels sequentially multiplies this effort.	**Reduced administrative burden** A single WES/WTS test requires ordering, financing, and reporting only once.
Multiple partial reports The results of each panel are presented in a separate report, requiring additional time to consolidate, interpret, and prioritize results.	**Single comprehensive report** WES/WTS results are presented, interpreted, and prioritized in a single report, thereby streamlining the clinical decision-making process.

Table 1. Compared to running several multigene panels sequentially, WES/WTS offers a more efficient and cost-effective way to obtain the maximum information on a patient's cancer at the start of the patient journey. Multigene panels focus on a specific set of cancer-associated genes, potentially missing clinically relevant information.

WES/WTS Provides Value Across the Patient Journey

Two of oncology's most valuable resources, time and information, have historically come at the expense of one another due to cancer's rapidly progressive nature. Fast treatment initiation should logically drive better outcomes. However, starting treatment without all clinically actionable information may result in the use of non-beneficial therapies. Collecting all clinically actionable information can take time, though, especially when relying on sequential tests. Now, with the increasing availability and affordability of WES/WTS, a compromise between time and information is no longer necessary. Compared to running multiple DNA or RNA single or multigene panels sequentially, WES/WTS can deliver more information in less time, using comparable tissue, and at an only slightly higher upfront cost (**Table 2**).

Outcomes

Biomarker Testing Improves Outcomes for Cancer Patients

One of the first large-scale studies to demonstrate the benefit of genomic profiling for biomarker-linked therapies was the Initiative for Molecular Profiling in Advanced Cancer Therapy (IMPACT) study, which was started in 2007. The exploratory IMPACT study tested the hypothesis that therapy selection based on molecular profiling would improve clinical outcomes compared to standard therapy. Patients recruited to the Phase I study had exhausted all standard care options or had uncurable rare cancers.

Results from the IMPACT study showed that around 40% of enrolled patients had at least one targetable alteration.[30] Patients who went on to receive a molecularly matched therapy had significantly better overall response rates (ORRs), longer time to treatment failure, and longer survival. The subsequent IMPACT2 randomized trial found that matched targeted therapies are also associated with longer progression-free survival (PFS) than standard, non-matched treatments.[31]

Since IMPACT, numerous studies have demonstrated that biomarker testing and matched targeted therapies improve patient outcomes **(Figure 5)**. An evaluation of the effect of Caris' tumor molecular profiling on survival showed that outcomes are better when patients receive biomarker-matched drugs across a range of cancer types.[32] Patients whose treatments matched those predicted by profiling to be beneficial lived longer than those that did not, with two-thirds of the molecularly matched patients still alive at the end of the study period compared to only half in the unmatched group. In addition to reduced mortality, molecularly matched patients also received fewer treatments than unmatched patients. In roughly nine out of ten Caris WES/WTS-tested patients, their pre-testing treatment plan was changed in response to profiling results.[33]

Current ASCO guidelines recommend that patients with advanced and metastatic solid tumors undergo molecular profiling when there are approved biomarker-linked therapies and support the rationale for testing all solid tumors based on site-agnostic drug approvals.[5] Broad DNA profiling of multiple biomarkers is the guideline-recommended standard of care in many cancers, including aNSCLC. More than 15 FDA-approved targeted therapies are available for biomarker-positive patients with aNSCLC. These therapies have ORRs in the 60-80% range and PFS of 9-34 months, compared with 20-45% ORR and 5-6 months PFS in patients receiving standard chemotherapy.[34]

Adding RNA sequencing to DNA analysis can increase treatment options for patients.[14,15] In a recent study, 16% (36/232) of NSCLC cases negative for oncogenic drivers by standard DNA analysis were found to be positive by RNA sequencing, with the majority (33/36) clinically actionable.[16] Furthermore, the addition of transcriptomic profiling to DNA analysis led to 35% of patients receiving a matched targeted therapy in the WINTHER trial. Without RNA analysis, only 23% of patients would have received matched treatment.[35]

ASCO guidelines recommend RNA-based fusion testing for patients when no oncogenic drivers have been identified through multigene panel-based DNA sequencing and in those without standard care options.[5] Fusion testing is also strongly recommended if approved fusion-targeted, disease-specific therapies are available for a patient's metastatic or advanced cancer.[5] Additionally, outside of disease-specific approvals, patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy should undergo NTRK fusion testing.[5]

Companion Diagnostics Help Improve Outcomes

Companion diagnostics are FDA-regulated biomarker tests that indicate benefit/non-benefit for a specific drug. For example, the PD-L1 test is the best predictor for PD-L1 targeted therapy response. FDA-approved companion diagnostic (CDx) PD-L1 assays are available for a range of cancers and drugs. One such assay predicts response to pembrolizumab, an immunotherapy drug.[37] In advanced NSCLC patients with PD-L1 expression in ≥50% of cells, pembrolizumab is associated with better outcomes than chemotherapy.[38]

In a study of 17,555 patients with non-squamous advanced NSCLC, patients who received CDx testing lived longer than those who were not tested (median survival 13 months versus six months). This survival benefit was even more pronounced in the patients who then received biomarker-driven therapy as their first line of treatment, with a median survival time of 18 months in the tested patients compared to 6 months in untested patients.[39]

CDx tests are designated as medical devices because they generate information essential for the safe and effective use of, and help decide which patients should receive, the corresponding therapeutic.[1] While important for therapy selection, it should be noted that current professional guidelines do not require biomarker tests to be FDA-approved, but only to be performed by a CLIA certified laboratory.

Clinical Utility, Now and in the Future

As oncology transitions from universal to personalized treatment, hotspot and multigene panels are increasingly insufficient. WES/WTS, however, continuously evolves to keep up with the latest research, treatments, and trials to provide clinically actionable insights. Moreover, the extensive molecular blueprint generated by WES/WTS facilitates the future use of as-yet-undiscovered biomarkers and therapies.

~1 in 2 cancer patients has a detectable actionable mutation.[36]

Patients who receive a biomarker-matched therapy have significantly better outcomes than those with non-matched treatments.[30]

28

biomarker-targeted drugs were approved by the FDA in 2020.[5]

9 in 10 new breast cancer drugs approved by the FDA in 2009-2018 were biomarker-targeted.[10]

Comprehensive profiling reduces the likelihood of missing targeted therapy options compared to smaller tests.[7]

Broad profiling of multiple biomarkers is guideline-recommended standard of care in many cancers.[34]

Figure 5. Biomarker testing and matched targeted therapies improve patient outcomes. Studies support and clinical guidelines recommend broad molecular profiling for solid tumors.

Time

When multigene panel or other non-comprehensive profiling approaches fail to detect clinically actionable alterations in a patient's cancer, oncologists are faced with settling for standard, non-targeted treatments or retesting using another method. The second option keeps the door open for potential biomarker-directed therapies but at the expense of time to treatment. Testing with multiple sequential panels can greatly increase the time to an actionable result **(Figure 6)**.

Delayed profiling results can significantly impact patient outcomes. In a retrospective study of >500 aNSCLC patients later found to have actionable oncogenic driver mutations, 27% of patients commenced standard treatment (chemotherapy, immune checkpoint inhibitors, or both) before receiving their NGS results.[40] Outcomes were significantly compromised in these patients, even in the subgroup that switched to a tyrosine kinase inhibitor upon receiving their results. Rapid generation of comprehensive profiling results is, therefore, of paramount importance and is enabled by WES/WTS.

Proponents of multigene panel testing often counter that, in situations where testing returns an actionable result the first time, further testing is not needed and results are produced faster than WES/WTS. However, these potentially quicker results are not comprehensive and may be missing critical findings, leading to incorrect treatments and worse outcomes at increased financial costs. Waiting a few days longer for optimal results is advisable, and, indeed, patients may be amenable. A multinational survey of cancer patients reported that two-thirds (66%) were willing to delay treatment to allow for additional testing, with 22% willing to wait a month and 32% saying they would delay as long as it takes to get results rather than starting treatment without them.[41]

Specimen

In addition to wasting valuable time, the failure of non-comprehensive assays to detect actionable alterations can limit further testing options **(Figure 6)**. Following non-comprehensive testing, there may be insufficient tissue remaining for comprehensive profiling. Data presented at the 2023 ASCO Annual Meeting showed that prior negative single gene testing reduces the chance of obtaining a result from subsequent CGP.[42] When CGP was used as a second versus first-line test, the number of CGP test cancellations doubled due to tissue insufficiency and related increased DNA sequencing failures. This finding is of particular concern for cancers with limited tissue access and availability, such as NSCLC, and in situations where frontline therapy fails and further biopsies are not feasible. WES/WTS solves this issue by maximizing the actionable information obtained at the start of the patient journey.

Cost

Biomarker-driven therapies not only improve outcomes but can also decrease healthcare costs. In a survey of medical claims for lung cancer care, patients who underwent broad panel testing and thus received more optimal treatment had a ~$8,500 monthly health expenditure saving compared to patients who received treatment indicated by a small multigene panel.[8]

in overall total cost of care due to more optimal treatment in patients who received broad versus narrow panel testing.[8]

Incorporation of WES/WTS into clinical practice promises even more considerable savings. By identifying all known actionable biomarkers at initial diagnosis, WES/WTS has unrivaled power to guide therapy selection. WES/WTS enables clinicians to match patients to the right treatment the first time and reduce time spent on and unnecessary side effects from ineffective therapies. In the long run, WES/WTS can reduce healthcare costs by improving patient outcomes and minimizing the need for and associated costs of subsequent lines of therapy. Patients who receive molecularly matched treatments identified as beneficial by Caris molecular profiling not only have improved survival, but also receive fewer treatments than those receiving unmatched therapies.[32] WES/WTS-based biomarker detection can also aid in identifying aggressive or treatment-resistant cancers, enabling clinicians to tailor treatment appropriately and thereby potentially avoiding advanced or metastatic forms of the disease and limiting associated healthcare costs.

When non-comprehensive molecular profiling tests miss clinically actionable findings, additional testing must be ordered if a clinician wishes to find actionable biomarkers. The financial burden of ordering multiple sequential panels and potentially additional biopsies can outweigh WES/WTS' initially higher outlay **(Figure 6)**. A cost-comparison analysis based on Caris' WES/WTS showed that, due to overall improved survival, the additional cost of performing WES/WTS is cost-effective in the long run. Furthermore, results from Caris' profiling changed the treatment plan in 88% of cases.[33] The downstream costs associated with missing findings and providing suboptimal treatment can be substantial from both a monetary and quality-of-life perspective.

A final mechanism through which WES/WTS offers potential cost savings is by enabling the matching of patients to clinical trials for biomarker-targeted therapies. Once enrolled in trials, patients may be able to access otherwise unaffordable treatment. Similarly, removing patients from mainstream healthcare reduces the financial burden on payors and health systems, transferring costs to the trial sponsors.

OUTCOMES	WES/WTS enables clinicians to gather the most biomarker information from a single specimen, maximizing the likelihood of matching patients to targeted therapies and thus improving outcomes.
TIME	WES/WTS and individual multigene panels take a similar length of time to run. When sequential multigene panels are needed, however, the time to an actionable result is longer than for WES/WTS. In addition, WES/WTS provides more data earlier in the patient journey.
SPECIMEN	WES/WTS derives the maximum data from a single patient specimen. When an initial multigene panel fails to detect actionable biomarkers, additional specimens may be needed to conduct further testing.
COST	The additional testing required when panels fail to detect actionable biomarkers costs more cumulatively than the initial outlay for WES/WTS. Moreover, the downstream costs from missing actionable findings can be high.

Table 2. WES/WTS offers increased value to physicians, patients, and payors. Compared to multigene panel testing, WES/WTS extracts more information from a single sample. Incomplete genomic coverage by smaller panels often necessitates the sequential running of multiple tests, which may lead to a longer time to an actionable result, increased sample requirements, and potentially higher overall cost.

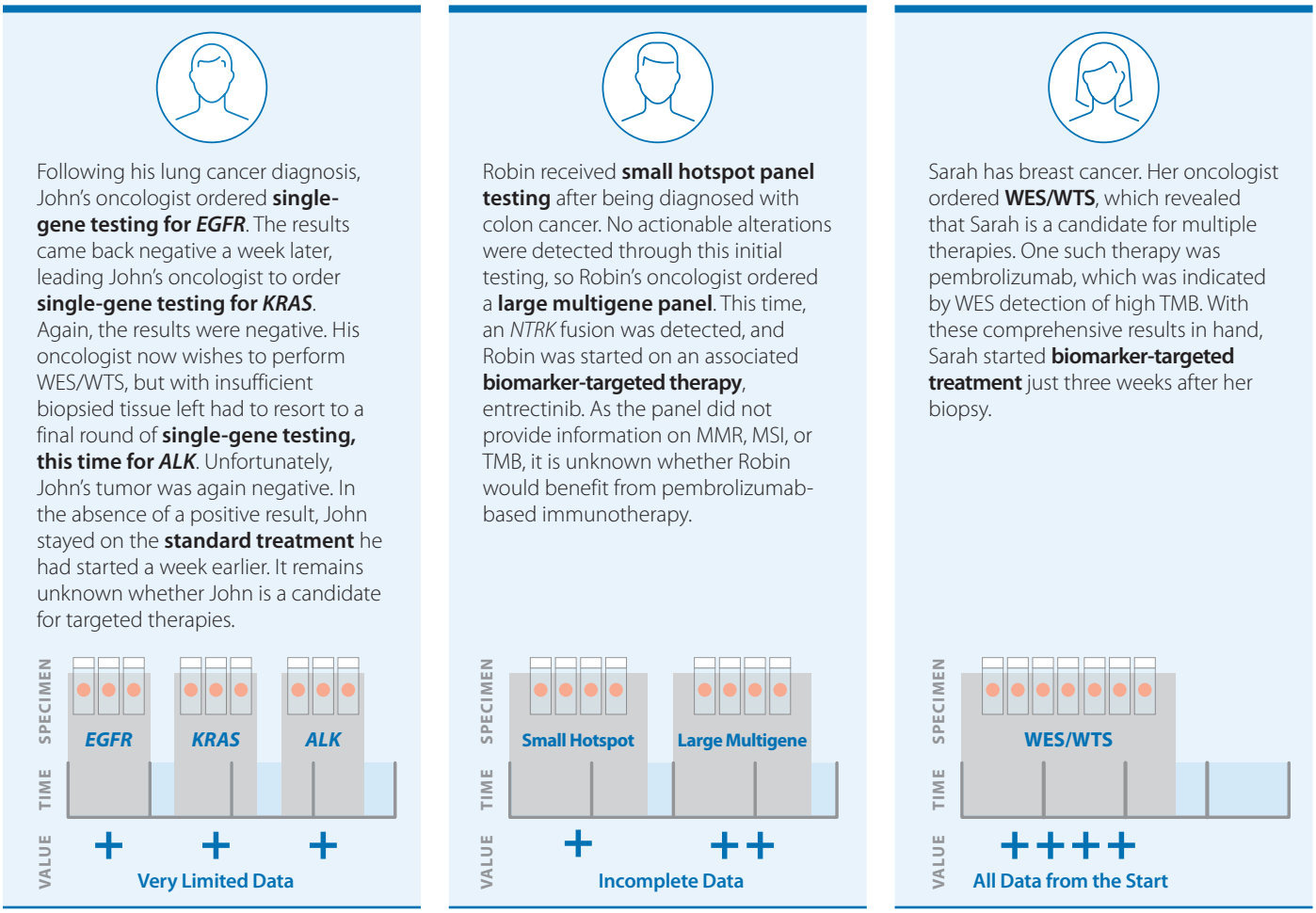


Figure 6. Compared to running multiple sequential tests or panels, WES/WTS can offer more comprehensive results in less time, using comparable specimen, and at relatively little additional cost. These three example patient journeys illustrate the benefits of using a comprehensive profiling approach upfront. The amount of patient tissue used is represented by slide icons. Each vertical line in the timeline represents one week. The time taken to run tests is shown as gray shading, with the gaps between sequential tests representing time taken to order new tests. Testing value is denoted by plus signs. These examples are illustrative and not precise.

WES/WTS Simplifies Clinical Decision-Making

In a single test, WES/WTS provides all the information needed to guide the best clinical decisions. WES/WTS enables accurate identification of actionable genomic alterations that can be leveraged to match patients to the most effective treatments, yielding a higher probability of response and providing comprehensive predictive and prognostic information. Cumulatively, WES/WTS insights empower clinicians to make the most informed choices for their patients **(Figure 7)**. Furthermore, the benefits conferred by WES/WTS extend across the healthcare ecosystem, beyond just clinicians and their patients. By supporting WES/WTS, payors can reduce waste and harm from suboptimal profiling and resulting treatments **(Figure 8)**.

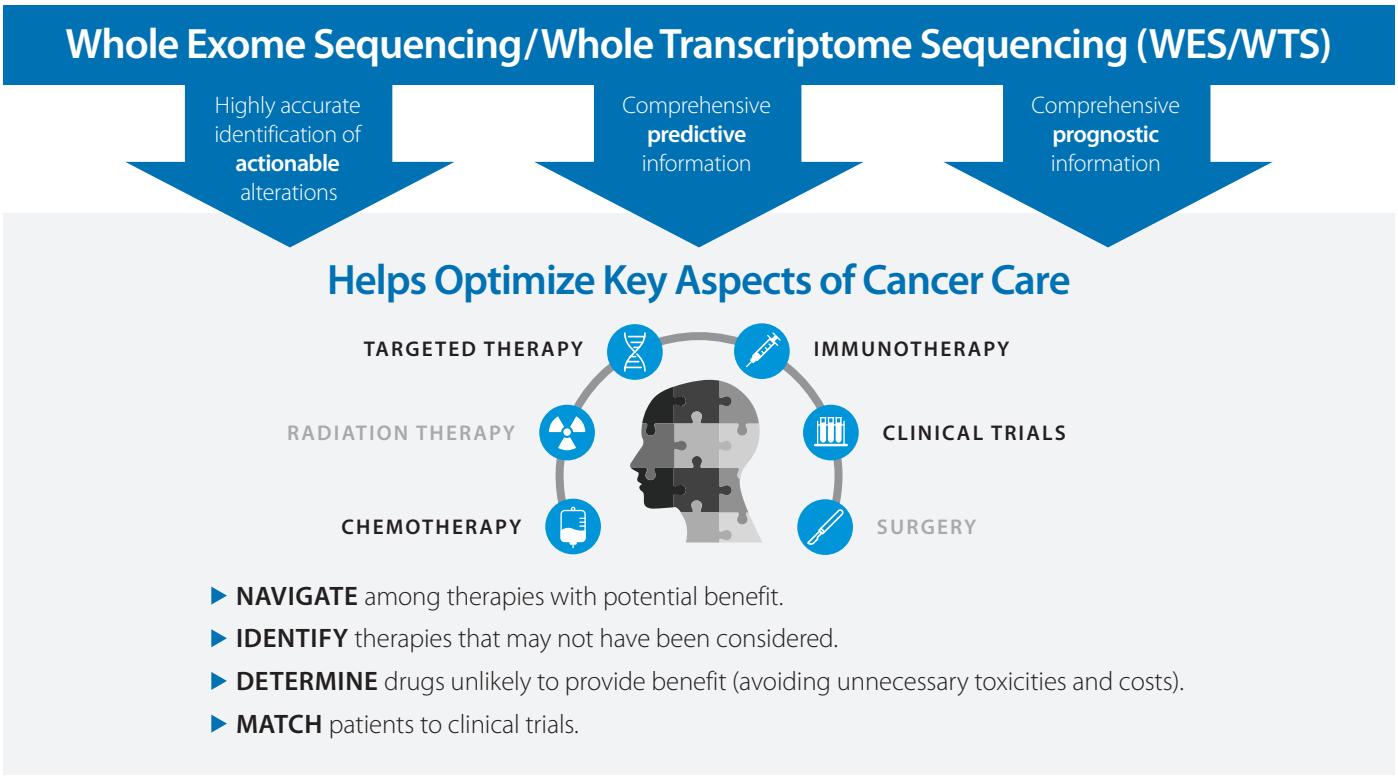


Figure 7. WES/WTS empowers clinicians to answer the question, "What are the treatment options for my patient and how can I enable the best possible outcome?" As part of a comprehensive care plan, a single WES/WTS test can guide diagnosis, prognosis, and the selection of biomarker-associated therapies and clinical trials.

How can payors reduce the waste and harm of oncology treatments?

Figure 8. WES/WTS enables healthcare payors to reduce potential waste and harm from cancer care, while optimizing patient outcomes. By ensuring that each patient gets the most appropriate drug the first time, WES/WTS reduces clinical guesswork.

Which Patients Should Receive WES/WTS?

Large-scale studies have shown that actionable mutations can be detected in around 40-50% of patients,[25,30,36] meaning that molecular profiling has potential clinical utility in a significant proportion of cases. A recent ASCO Provisional Clinical Opinion underscored the importance of somatic genomic testing in patients with metastatic or advanced cancer. ASCO recommends that patients with advanced and metastatic solid tumors undergo molecular profiling when there are approved biomarker-linked therapies and supports the rationale for testing all solid tumors based on site-agnostic drug approvals.[5] Furthermore, the ASCO guidelines outline several clinical situations which may merit WES/WTS **(Table 3)**. NCCN also supports broad biomarker testing, which is covered by WES/WTS. **Table 4** outlines the NCCN guidelines for breast, prostate, lung, and colorectal cancer, which together account for half of all new cancer cases in 2023.[50]

POPULATION	ASCO RECOMMENDATION[5]
Patients under consideration for immunotherapy	TMB is a predictive biomarker for immunotherapy response. The ASCO guidelines note that WES is the gold standard to measure TMB.
Patients with no oncogenic drivers detected by DNA analysis	ASCO recommends using RNA-based fusion testing, including WTS, for these patients.
Patients without other standard care options	ASCO recommends RNA-based fusion testing, including WTS, for this population.
Patients with cancer of unknown primary (CUP)	Specific mutational signatures can help identify tumor origin. ASCO notes that these signatures, and other features, such as TMB and gLOH, are best measured by WES or WGS.
Patients with rare cancers	Mutational signatures can also help classify rare cancers. WES or WGS are the best methods to measure these signatures.

Table 3. Current ASCO recommendations for WES/WTS. A recent ASCO Provisional Clinical Opinion highlighted the importance of somatic genomic testing in patients with metastatic or advanced cancer.[5]

CANCER TYPE	NEW CANCER CASES (2023)[52]	NCCN GUIDELINES™ FOR BIOMARKER TESTING	
		Biomarker(s)	**Clinical scenario**
Breast[53]	15%	HER2	All new primary or newly metastatic breast cancers.
		HR (ER and PR)	Any new primary or newly metastatic breast cancer.
		PIK3CA, ESR1	HR+ HER2- recurrent unresectable or stage IV disease.
		NTRK fusions, MSI-H/dMMR, TMB-H, *RET* fusions	Any subtype.
		Somatic: HER2, *BRCA1/2*, Germline: *PALB2*	Stage IV disease – emerging biomarkers.
Prostate[54]	15%	HRR genes such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12*	Recommended: Metastatic prostate cancer (mPC). Considered: Regional PC.
		MSI-H/dMMR	Recommended: Metastatic castration-resistant prostate cancer (mCRPC). Considered: Regional or castration-sensitive mPC.
		TMB	Considered: mCRPC.
Lung & Bronchus[55]	12%	*EGFR, ALK, ROS1, BRAF, KRAS, MET, RET, ERBB2, NTRK fusions*, and PD-L1	Non-small cell lung cancer (NSCLC). In NSCLC patients without driver oncogenes identified by broad panel testing, consider RNA-based NGS to maximize detection of fusion events.
Colon & Rectal[56]	8%	*KRAS, NRAS, BRAF,* HER2, MSI-H/dMMR, and *NTRK* fusions	Metastatic colorectal cancer (mCRC). NGS has the advantage of picking up rare actionable alterations, such as *NTRK* and *RET* fusions.

Table 4. Current NCCN guidelines for biomarker testing. For the four most common cancers, NCCN recommends testing for a range of biomarkers. *Data reflects guidelines as of September 2023.*

Conclusion

In summary, WES/WTS represents a paradigm shift in oncology that provides immense clinical and economic value to patients, clinicians, and payors. A comprehensive profiling approach leaves no molecular stone unturned to provide oncologists with the information necessary to take advantage of today's most advanced treatments while futureproofing their patient's treatment journey. When utilized as part of a complete cancer care plan, information generated by WES/WTS can translate into improved patient outcomes and reduced time on ineffective therapies. Moreover, WES/WTS has long-term economic benefits as avoidance of ineffective treatments can minimize unnecessary costs and enable cost-effective utilization of resources.

Currently, many patients do not receive WES/WTS and are under-profiled for biomarkers with FDA-approved therapies. However, as technologies evolve and become more cost-effective, WES/WTS will be able to continue to improve outcomes for a larger number of patients.[2] Integrating WES/WTS into clinical oncology will not only optimize care but also lay the foundation for a more efficient and cost-conscious approach to cancer treatment. Adopting WES/WTS as the standard of care is a crucial step towards advancing precision oncology and improving the lives of cancer patients.

Future Frontiers in Precision Oncology

Liquid Biopsy

There is growing interest in liquid biopsy as a less invasive alternative to tumor biopsies to increase the clinical use of WES/WTS for the screening, profiling, and serial monitoring of cancer. Liquid biopsy enables biomarker monitoring at multiple timepoints and clinical stages, including early detection, therapy selection, response monitoring, and disease recurrence monitoring. In studies, liquid biopsy performs well, with demonstrated concordance between tissue and blood profiling results[57,58] and non-inferiority of circulating cell-free DNA (cfDNA) in detecting guideline-recommended biomarkers.[34] Analyzing cfDNA in addition to tissue increases detection of patients with an identified guideline-recommended biomarker by 48%.[57] While tissue remains the gold standard for WES/WTS, and clinical guidelines defer to tissue unless the specimen is exhausted, this preference may shift once clinical trials demonstrate further clinical value.

AI and Big Data

The next stage in oncology's evolution will involve data – and lots of it. There are currently oceans of clinical and molecular patient data, which are exponentially expanding as WES/WTS becomes more common. Artificial intelligence (AI)-driven analysis of these resources, in tandem with natural language processing and predictive modeling approaches, may be the next step in improving outcomes. AI will likely be employed to extract molecular insights, identify novel biomarkers, develop new drugs, and accurately predict patient trajectories.

Complex Biomarkers

Precision oncology is already moving beyond single predictive biomarkers and into the realm of more complex features, such as mutational signatures, complex molecular networks, and epigenetics.[25] AI is likely to play a critical role in identifying these complex biomarkers and developing targeted therapies based on them.

WES/WTS Accessibility

There is a significant disconnect between advances in targeted therapies and delivery of these therapies to patients. This disparity may compound existing health disparities, with socioeconomic differences increasingly a factor in access to profiling.[59] To improve access and ensure broad adoption, it is critical that WES/WTS is incorporated into clinical practice guidelines and its clinical value demonstrated to encourage payor coverage and limit health disparities. Education and clinical support tools will also be central to establishing WES/WTS as standard of care.

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Glossary

TERM	DEFINITION
Biomarker	Measurable biological characteristics that can identify, for example, which patients will have a certain response to an intervention.
Companion diagnostic (CDx)	FDA-regulated test for biomarkers associated with a specific therapeutic agent.
Genomic loss of heterozygosity (gLOH)	Genome-wide loss of previously heterozygous wildtype alleles of genes. gLOH is indicative of HRD.
Hotspot panel	Targeted panel covering actionable alterations commonly found in tumors.
Homologous recombination deficiency (HRD)	Inefficient repair of damaged DNA via homologous recombination.
Liquid biopsy	Analysis of a biological fluid, typically blood, to detect biomarkers and provide other molecular insights.
Matched Therapy	A therapy predicted to be beneficial based on a patient's molecular profiling results.
Microsatellite instability (MSI)	Presence of insertions or deletions at microsatellite loci. MSI is indicative of defective mismatch repair (dMMR).
Molecular profiling	Analysis of DNA or RNA from a biological sample.
Multigene panel	DNA (or RNA) test, usually NGS-based, for a specific set of cancer- and therapy-associated genes.
Next-generation sequencing (NGS)	A type of sequencing suited to accurate, high-throughput, large-scale genomic testing. Also known as massively parallel sequencing.
Precision oncology	The use of molecular biomarkers to assist in the diagnosis, prognosis, and treatment of cancer.
Targeted panel	DNA (or RNA) tests designed to detect a specific set of alterations or regions of interest across multiple genes (from a few to hundreds).
Targeted therapy	A therapy designed to selectively inhibit or promote death of cancer cells harboring a specific genomic alteration.
Tumor mutational burden (TMB)	Measurement of the number of somatic mutations per megabase of DNA sequenced.
Whole genome sequencing (WGS)	Sequencing of all the DNA in an individual's genome, including non-coding regions.
Whole exome sequencing (WES)	Sequencing of all the DNA exons (protein-coding regions) of genes in the genome.
Whole transcriptome sequencing (WTS)	Sequencing of all the transcribed RNA from the genes in the genome.

About Caris Life Sciences

Caris Life Sciences is the leading next-generation AI TechBio company and precision medicine pioneer actively developing and delivering innovative solutions to revolutionize healthcare and improve the human condition. Through WES/WTS and the application of advanced artificial intelligence (AI) and machine learning algorithms, Caris has created the large-scale, clinico-genomic database and computing capabilities needed to analyze and unravel the molecular complexity of disease. This convergence of sequencing power, big data, and AI technologies provides an unmatched platform to deliver the next generation of precision medicine tools for early detection, diagnosis, monitoring, therapy selection, and drug development.

Headquartered in Irving, Texas, Caris has offices in the US (Phoenix, New York, Denver), Japan (Tokyo), and Switzerland (Basel). Caris provides services throughout the US, Europe, Asia, and other international markets.

Caris is dedicated to increasing awareness of and expanding access to WES/WTS to improve patient outcomes. At the forefront of precision medicine from the start, Caris continues to set bold standards, having already achieved many important objectives:

- First WES/WTS service for oncology.
- First drug response AI predictor for mCRC.
- First biomarker-driven trial match service.
- Largest clinico-genomic database in case volume, biomarker depth, and real-world outcomes.
- More than 500,000 cancer patients profiled, with hundreds more tested each day.

The Caris laboratory has met rigorous quality standards, including CAP, CLIA, NYSDOH, and ISO15189 accreditation. MI Tumor Seek Hybrid™ has been demonstrated to detect guideline-recommended tumor-specific and tumor-agnostic biomarkers, identify appropriate therapies for individuals based on the presence/absence of specific mutations, and improve safety and clinical outcomes as a response.

Caris was issued the first patents on WES/WTS for its exclusive Caris molecular profiling technology. This includes the following U.S. Patent Numbers: 9,389,234; 9,322,067; 9,092,392; 9,064,045; 9,058,418; 9,053,224; 8,914,239; 8,831,890; and 8,700,335.

MI Tumor Seek Hybrid™* Assay

Whole Exome Sequencing (WES) DNA

- 23,000+ genes
- 1,500x for clinical genes
- SNVs, Indels, CNAs & Karyotyping
- Viral Pathogens
- gLOH, HLA genotype, HRD, MSI, TMB

Whole Transcriptome Sequencing (WTS) RNA

- 23,000+ genes
- 17 million read count
- Gene fusions and variant transcripts
- Novel translocation detection independent of intronic breakpoint

AI-Driven Signatures*

Caris FOLFIRSTai™ Chemotherapy response predictor that is intended to gauge a mCRC patient's likelihood of benefit from first-line FOLFOX+BV followed by FOLFIRI+BV, versus FOLFIRI+BV followed by FOLFOX+BV treatment.

Caris GPSai™ Cancer type similarity assessment that is intended to help identify the tumor of origin by comparing the molecular characteristics of the patient's tumor against 90 tumor types in the Caris database.

Additional Caris Services

Caris offers tumor-specific testing beyond NGS-based methods, including protein analysis by immunohistochemistry (IHC), DNA/RNA localization by *in situ* hybridization (ISH) and methylation analysis by pyrosequencing.

*Not available in all locations. Visit www.carisls.com for current availability.