illumina®

Comprehensive genomic profiling

Maximize the chances of identifying molecularly matched therapies.

One biopsy, one test, one report can lead to improved patient outcomes.

Enable precision medicine with comprehensive genomic profiling

Driven by targeted molecular therapies and immunotherapies, precision medicine offers an individualized approach that battles cancer at its core—the genome. As new oncogenic drivers are uncovered at an unprecedented rate, a testing method that can keep pace is needed. One method meeting this challenge is comprehensive genomic profiling, or CGP.

One test can make the difference

- Analyze hundreds of clinically relevant biomarkers simultaneously
- Assess DNA and RNA alterations, including SNVs, CNVs, indels, fusions, and splice variants*
- Measure TMB, MSI, and HRD[1-5]*

Maximize data from one biopsy

- Replace multiple single-gene tests or small hotspot panels with one comprehensive test
- Decrease the need to rebiopsy to obtain more data[6-8]
- Reanalyze data as new biomarkers are discovered

Get results faster

- Achieve a faster turnaround time with CGP than sequential iterative testing[9]

Receive actionable results

- Unlock potential opportunities for molecularly matched therapy regimens
- Identify potential eligibility for matched clinical trials

Using CGP to match patients with targeted or immunotherapies has been linked to improved clinical outcomes[10-15]

- Increased ORR*
- Increased OS*
- Increased PFS*

> "Comprehensive genomic profiling not only maximizes tissue utilization from often scant tumor biopsies, but it can produce biomarker information across all the biomarker classes and mutations that are required to get a comprehensive picture of the tumor...having a detailed picture of the tumor is certainly what makes decision treatment options easier for clinicians."
>
> **Jeff Conroy**
> Chief Scientific Officer, OmniSeq, and Director of Genomics Consortium Technologies, Roswell Park Comprehensive Cancer Center

*SNV, single nucleotide variation; CNV, copy number variation; TMB, tumor mutational burden; MSI, microsatellite instability; HRD, homologous recombination deficiency; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

A single biomarker can transform lives

Every year, promising cancer therapies are developed and approved, offering the potential for improved clinical outcomes for patients with qualifying cancer types. Many of these therapies are molecularly targeted, zeroing in on oncogenic drivers to fight the cancer at its source. As the number of biomarkers increases, it is critical to find ways to maximize the ability to match patients with appropriate molecular treatment regimens.

Many biomarker tests are available to aid with therapy selection. However, ordering individual, sequential biomarker tests requires a significant amount of biopsy sample that is not always accessible.[6-8] These single-gene tests screen for limited content and may miss the opportunity to identify a positive biomarker.

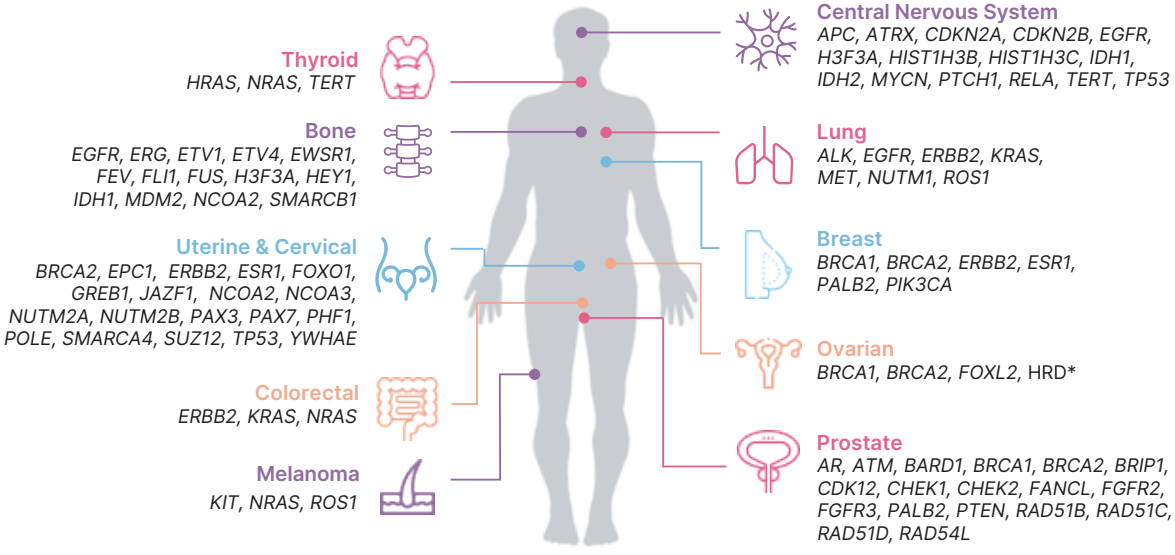
Identifying biomarkers is crucial

Over recent decades the underlying genomic drivers of many cancers have been revealed, creating a more complex picture of the disease than originally imagined. We now know that genetic variants can vary widely between histologically distinct tumors, and that heterogeneity can exist within a tumor itself. Moreover, tumors with similar driver mutations can have differing responses to therapies, adding additional complexity. This diversity makes it essential to understand the genetic makeup of each tumor.

COMPREHENSIVE GENOMIC PROFILING (CGP): a single assay that uses next-generation sequencing (NGS) to assess relevant cancer biomarkers, as established in guidelines and clinical trials, and inform therapy guidance. CGP detects biomarkers at nucleotide level–resolution and may comprise all major genomic variant classes (SNVs, indels, CNVs, fusions, splice variants), and large genomic signatures (TMB, MSI, HRD), maximizing the ability to find clinically actionable alterations.

Biomarkers in US guidelines and drug labels for highly prevalent tumors[16,17]

Solid tumors (pan-cancer): *BRAF, NTRK1, NTRK2, NTRK3, RET,* TMB, MSI

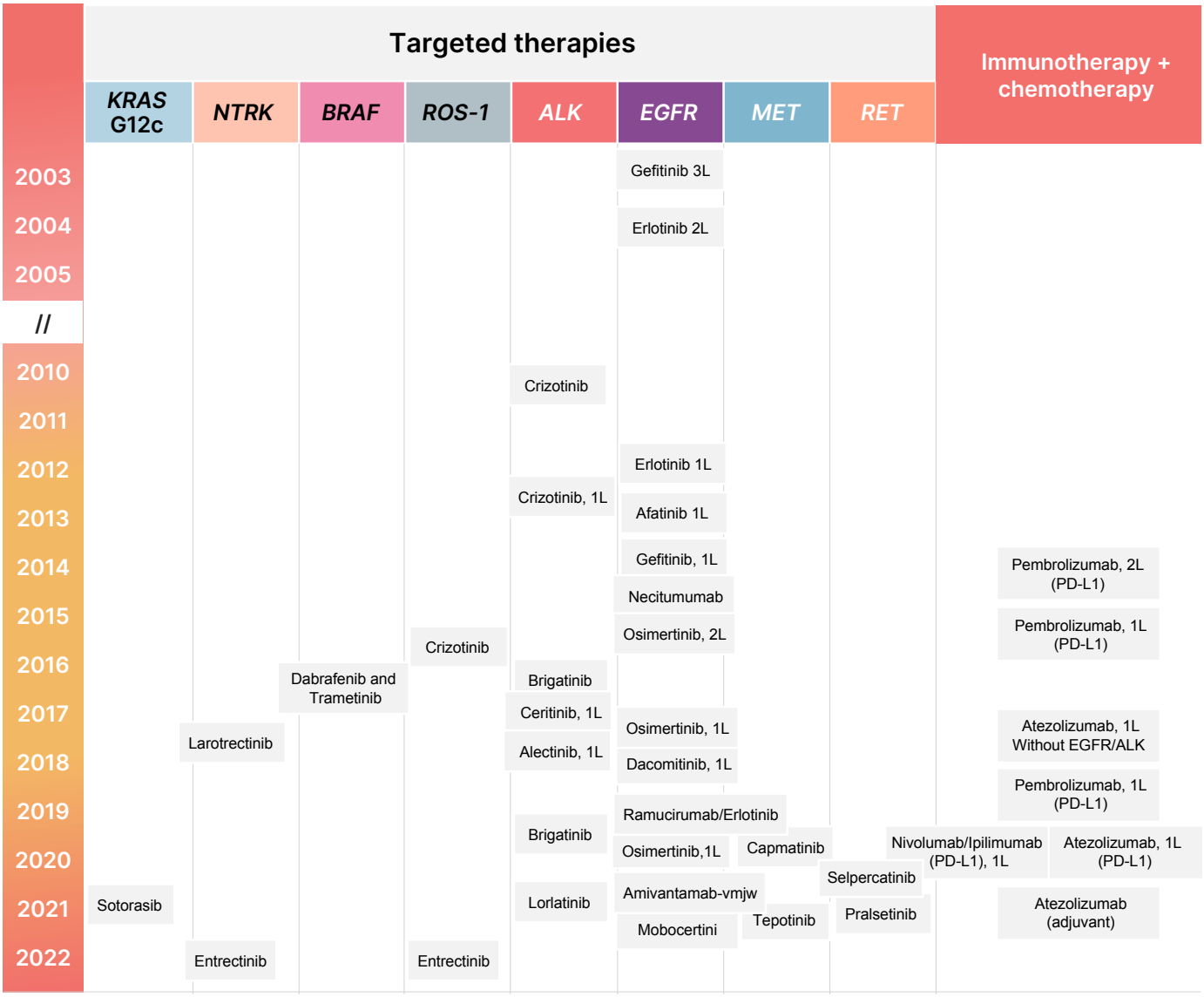


Based on evidence in scientific literature, presence in clinical trials, or linked to labels in other histologies.
*In ovarian cancer, HRD is noted as a molecular signature based on a measurement of genomic instability.

Biomarker-driven therapy selection

Currently, 650+ drugs are listed on the National Cancer Institute cancer treatment website.[18] Clinicaltrials.gov lists over 4200 biomarker-linked trials in progress, globally, for all cancer types.* With 64% of available biomarker-driven therapies for non-small cell lung cancer (NSCLC) gaining US FDA approval in just the past five years,[16] it is clear that the pace of discovery is growing exponentially. The ability to detect these new biomarkers can match patients with targeted therapies, potentially leading to improved outcomes.[10-15]

Approved biomarker-driven therapies available for NSCLC treatment[16]



US FDA-approved indications of NSCLC treatments since 2003. Abbreviations: 1L, first-line; 2L, second-line; *ALK*, anaplastic lymphoma kinase; *BRAF*, murine sarcoma viral oncogene homolog B; *EGFR*, epidermal growth factor receptor; FDA, Food and Drug Administration; NSCLC, non–small cell lung cancer; *NTRK*, neurotropic tropomyosin receptor kinase; *PD-L1*, programmed-death ligand 1; *ROS-1*, c-ros1 oncogene.

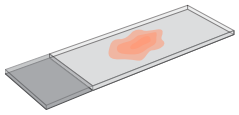
* Based on a search at clinicaltrials.gov using a combination of the terms "genetic," "genomic," "DNA," and "RNA." Accessed May 18, 2023.

TMB and MSI predict response to immunotherapy

Clinical trials and regulatory approvals have established several cancer immunotherapy treatments for multiple tumor types.[19] The ability to identify genomic signatures that help predict response to these treatments is important for better predicting patients who will benefit from these treatments. Tumor mutational burden (TMB) and microsatellite instability (MSI) status are two biomarkers that may predict patient response to immunotherapy and recommended for testing by select guidelines.

TMB measures the number of mutations in the coding sequence of the genome. In fact, 13-26% of advanced cancer patients exhibit TMB-High results across tumor types.[20-24] Accurately measuring TMB requires a large panel[25] and cannot be performed using small targeted panels that lack sufficient gene coverage.

MSI measures changes in DNA base repeats that may occur within the tumor. MSI status is FDA-approved for selection of solid tumors for treatment with checkpoint inhibitors.[26,27] Using CGP allows for analysis of a greater number of microsatellite loci than other methods, presenting opportunities to identify new MSI profiles in previously uncharacterized cancer types.[28]



Not all NGS panels are the same: Large assays with ~1.1 Mb of coding genome are needed to assess TMB accurately[1,25]

"tbNGS [tumor-based next-generation sequencing] can provide important clinical information and has the potential to improve patient outcomes when results are effectively integrated into treatment planning."

Foster KI, et al.[29]

About HRD

As researchers learn more about the underlying genomics of cancer, they are uncovering broader genomic signatures that may occur across cancer types. Homologous recombination deficiency (HRD) is a genomic signature of increasing importance in tumor biology for ovarian, breast, pancreatic, and prostate cancers. Patients with a tumor exhibiting HRD (HRD+) may be eligible for targeted PARPi therapies.[30,31]

Poly (ADP-ribose) polymerase inhibitors (PARPi) are a class of targeted therapies that may be prescribed to ovarian cancer patients with tumors that exhibit HRD.[32-35]

Genomic scarring and GIS

HRD results from a cell's inability to repair double-stranded DNA breaks using the homologous recombination repair (HRR) pathway. Double-stranded breaks are either not repaired or repaired using the error-prone nonhomologous end joining (NHEJ) pathway. These alternatives can lead to genomic instability, in the form of genomic scars, resulting in tumorigenesis.[36]

Genomic scars are aberrations that result in structural changes to the chromosomes, including loss of heterozygosity (LOH),[37] telomeric-allelic imbalance (TAI),[38] and large-scale state transitions (LST).[39] Each genomic scar can be measured alone, or summed together to produce a genomic instability score (GIS).

Determining HRD status

HRD status can be determined by evaluating the presence of causal genes (*BRCA* and other HRR genes) and/or the effect of genomic scarring. There is increasing evidence that assessing all three genomic scars (LOH, TAI, LST), along with causal genes, may maximize identification of HRD+ samples.[40-42]

HRD + CGP may provide added context to a disease

HRD status may reflect tumors positive for *BRCA* status and/or with a high GIS but does not address genomic variants beyond these factors. CGP can potentially identify additional biomarkers that may match patients with approved therapies or open clinical trials. By combining HRD assessment and CGP, clinicians can understand the full biology within a tumor, possibly leading to improved patient outcomes.

To learn more, read *Powerful insights from combining HRD and CGP*[43]

Loss of heterozygosity (LOH)

One of the two alleles for a gene is lost, creating a homozygous cell. This may result in malignant cell growth if the remaining allele does not function properly.

Telomeric-allelic imbalance (TAI)

The allele ratio at the end of the chromosomes (telomeres) in a pair do not match. That is, one chromosome has a greater number of alleles than the other.

Large-scale state transitions (LST)

Breakpoints between regions of the chromosome resulting in discrepancies within the chromosome pair.

Current testing methods may leave patients behind

Single-gene and small hotspot panel testing methods are limited in their ability to detect known and emerging biomarkers and molecular signatures, potentially missing important actionable variants.[6,44-46] CGP provides broad coverage of the genome, capturing a comprehensive set of clinically relevant genes in one test. Based on NGS, CGP detects DNA and RNA variants, including key genomic signatures, maximizing the ability to detect actionable variants compared to conventional methods.[6,10,25,45-49] The evaluation of RNA fusions and splice variants through RNA-based NGS assays is increasingly being recommended by clinical guidelines and associations.[50,51]

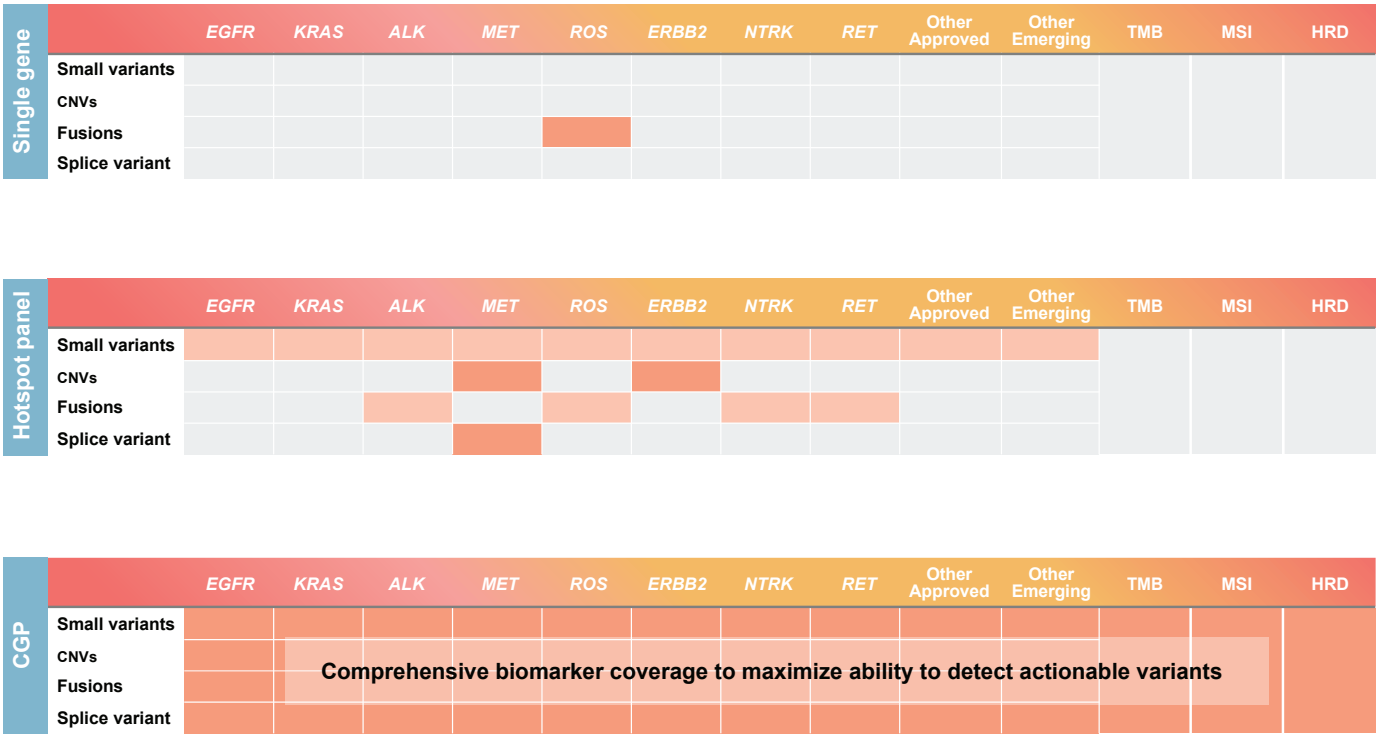
> "Single analyte tests or hotspot panels that are limited to a single gene or a few hot spot regions have really no potential to expand and keep up with the emerging markers, nor do they have the ability with their small footprint to do the larger signatures, such as MSI, TMB, and HRD."
>
> **Jeff Conroy**
> Chief Scientific Officer, OmniSeq and Director of Genomics Consortium Technologies, Roswell Park Comprehensive Cancer Center

Small hotspot panels can miss

81%

of actionable biomarkers in patients with refractory cancers, based on study with 10,000 patients[10]

CGP tests can increase the number of relevant biomarkers identified compared to conventional testing approaches, such as single-gene tests and hotspot NGS panels[6,10,45,47,48]



A missed biomarker is a potential missed opportunity

CGP provides a single test that uses minimal biopsy samples for deep analysis of biomarkers and molecular signatures linked to therapies, guidelines, and clinical trials. Data from CGP tests can be reanalyzed as new discoveries emerge, without the need to rebiopsy or to rerun the test.

> With CGP, every discovery is a potential opportunity.

Multiple studies have demonstrated the ability of CGP to identify clinically relevant genomic alterations, across different tumor types

Author	Study details	Patient cohort	Percent of patient samples with actionable variants identified[a]
Wheler JJ, et al 2016[52]	Prospective, single-center	339 patients profiled; refractory cancers, multiple types: ovarian (18%), breast (16%), sarcoma (13%), renal (7%), and others	93.5%
Hirschfield KM, et al 2016[53]	Prospective	100 patients; diverse histology rare, or poor-prognosis cancers	94.5%
Zehir A, et al 2017[10]	Prospective	10,000 patients; advanced cancer across multiple solid tumor types	36.7%
Reitsma M, et al 2019[47]	Retrospective	96 patients; multiple tumor types	90%
Foster K, et al 2022[29]	Retrospective	409 patients; high-grade epithelial ovarian carcinoma	74.6%

a. The percent of actionable alterations identified in each study varies according to patient cohort, study type, CGP panel used, and criteria for categorizing a genomic alteration as actionable.

Consolidate testing for more insights

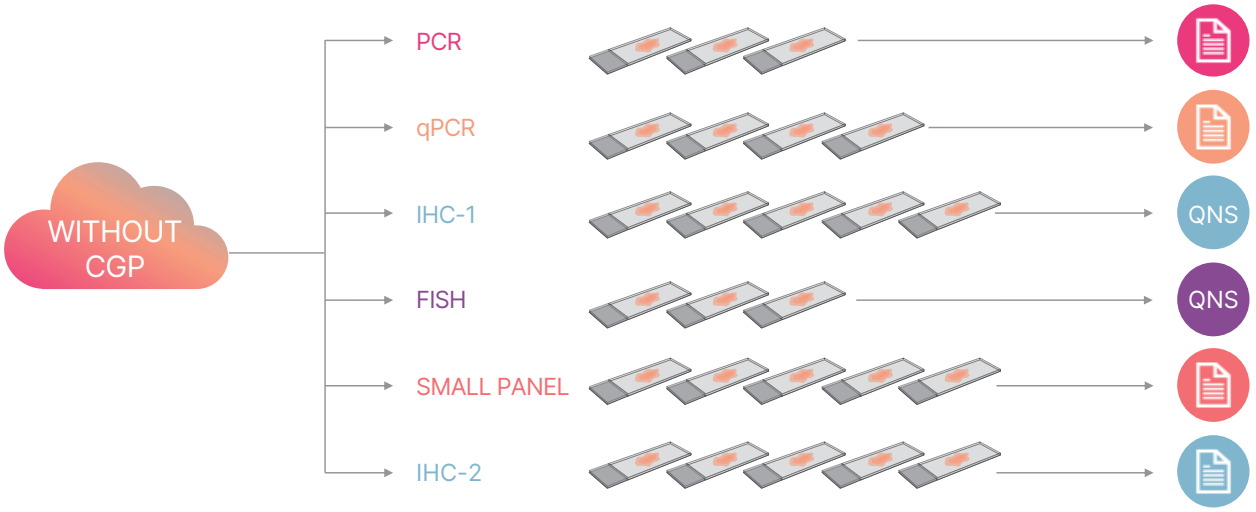
CGP replaces the need to run multiple independent tests with one consolidated test. This optimizes biopsy usage compared to iterative single-gene testing approaches that lead to tissue depletion and repeat biopsies.[6-8]

Identify more genomic variants from less sample

"The change from single-gene or single-biomarker testing to a comprehensive panel–based approach has been driven by a combination of factors that include inherent efficiency of a single comprehensive panel, which is key among cancers and other samples that have limited tissue."

Dr. Jeremy Wallentine
Staff Hematopathologist and Medical Director of Molecular Testing, Intermountain Healthcare

CGP provides actionable information for therapy selection from one test, one workflow, and one report



A comparison of potential workflows for patient sample analysis without (top) or with (bottom) CGP. Without CGP testing (top), the sample is spread across multiple tests, each one yielding a separate report, or none at all for tests that may require additional sample (QNS, quantity not sufficient). The CGP workflow (bottom) requires one test with as few as five slides and generates a single report that provides information on hundreds of biomarkers and includes guidance for possible therapies and clinical trials.

Stay current with guidelines

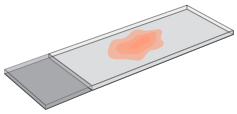
Cancer diagnosis and treatment guidelines are updated as new biomarkers are discovered, new therapies approved, and new clinical studies released. CGP can help with the challenge of keeping abreast of these developments. Large CGP panels provide significant coverage of known and emerging biomarkers in key guidelines for multiple tumor types and genes involved in clinical trials, providing access to comprehensive data in a single analysis. In fact, large panel NGS tests are increasingly being included in clinical guidelines and recommendations for biomarker profiling in multiple solid tumor types.[54] **NGS data are stored in a digital format that can be readily reanalyzed as new discoveries are made and approved, without the need for obtaining additional sample or running additional tests.**

> "It is highly recommended that clinical research centres perform multigene sequencing in the context of molecular screening programmes in order to increase access to innovative drugs and to speed up clinical research. This is particularly relevant in **breast, pancreatic, and hepatocellular cancers** where level II–IV alterations are numerous."
>
> – Mosele F, et al[54]

NGS tests are increasingly recommended by clinical guidelines for biomarker profiling in multiple solid tumor types.[55]
Tumor types in bold indicate TMB testing is recommended by clinical guidelines

Cancer types with NGS test recommendations		
Bladder	**Gastric**	Prostate
Bone	GIST	Rectal
Breast	**Head and neck**	**Salivary**
Cervical	**Hepatobiliary**	Small bowel adenocarcinoma
CNS	Lung adenocarcinoma	Soft tissue sarcomas
Cholangiocarcinoma	**Neuroendocrine and adrenal tumors**	**Testicular**
Colon	NSCLC	**Thyroid**
Colorectal	**Occult CUP**	**Uterine**
Cutaneous melanoma	**Ovarian**	**Vulvar**
Esophageal/esophagogastric junction	Pancreatic	

CNS, central nervous system; GIST, gastrointestinal stromal tumors; NSCLC, non-small cell lung cancer; CUP, cancer of unknown primary.



Not all NGS panels are the same: Large assays with ~1.1 Mb of coding genome are needed to assess TMB accurately[1,25]

CGP analyzes hundreds of biomarkers simultaneously, including MSI, TMB, and HRD

Guidelines recommend testing for up to

12

genomic biomarkers for NSCLC

Comprehensive genomic insights from one consolidated report

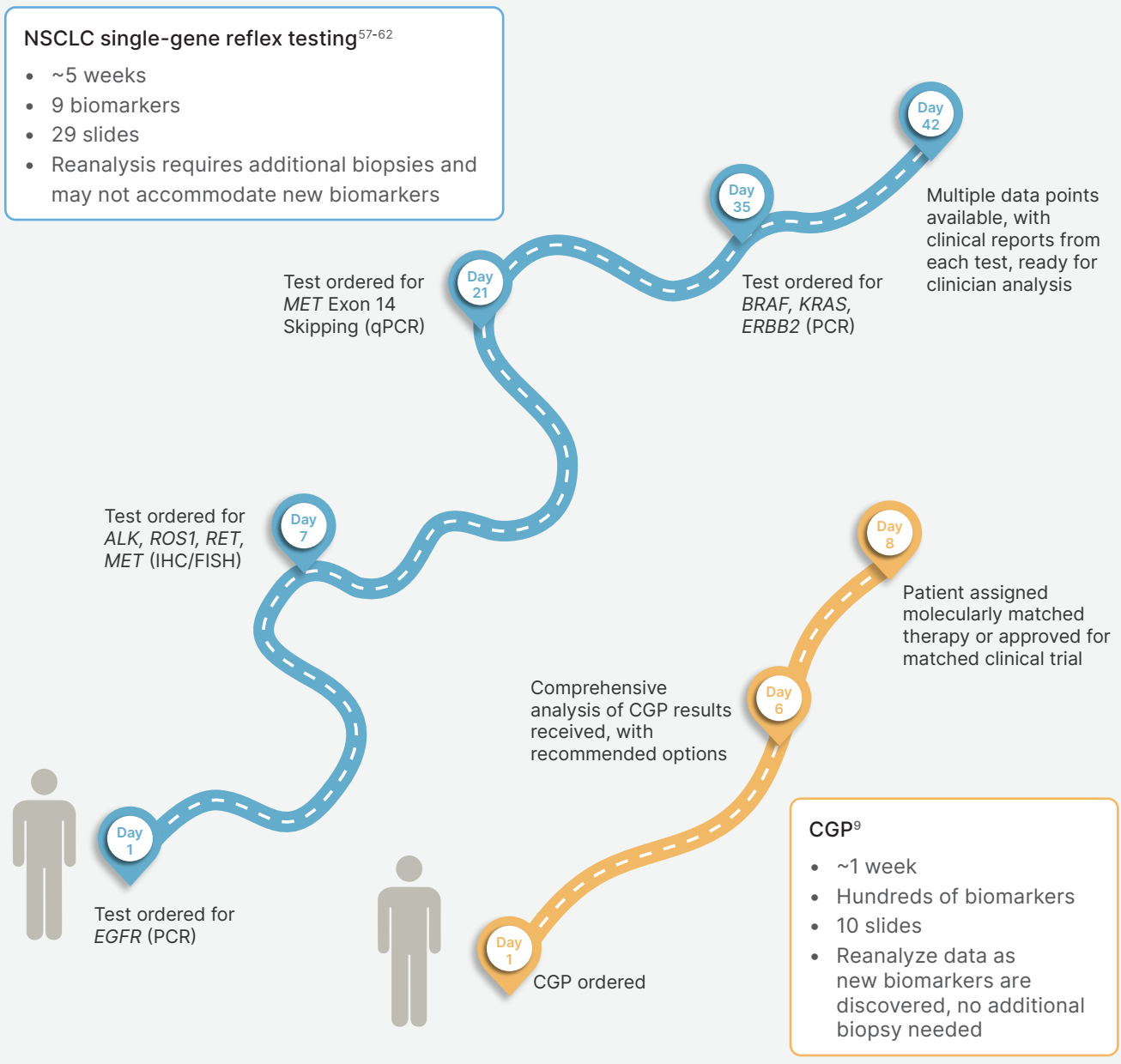
A CGP report may include a list of biomarkers identified by the tumor profiling assay and relevant information consolidated in one document. The user-curated report may include information on therapies associated with genetic variants identified through comprehensive tumor profiling. It also may indicate clinical trials linked to the detected biomarkers.[10,11,47,56]

> A single CGP report streamlines the workflow by including findings on genomic alterations specific to relevant biomarkers, targeted and immunotherapies specific to a tumor's genotype, and open clinical trials.

Therapy selection, sooner

By transforming the test-results-repeat paradigm experienced with sequential testing into a single consolidated test, CGP delivers results faster. One study describes a patient journey in which the patient went from CGP testing to therapy selection in just 8 days.[9]

Potential patient journeys



Comparison between a potential journey of a patient receiving in-house CGP with that of a patient receiving single-gene testing. Example illustrates single-gene testing based on an NSCLC patient. Test times and tissue requirements for the NSCLC example compiled from test menus offered by various medical laboratories.

The right therapy for the right patient

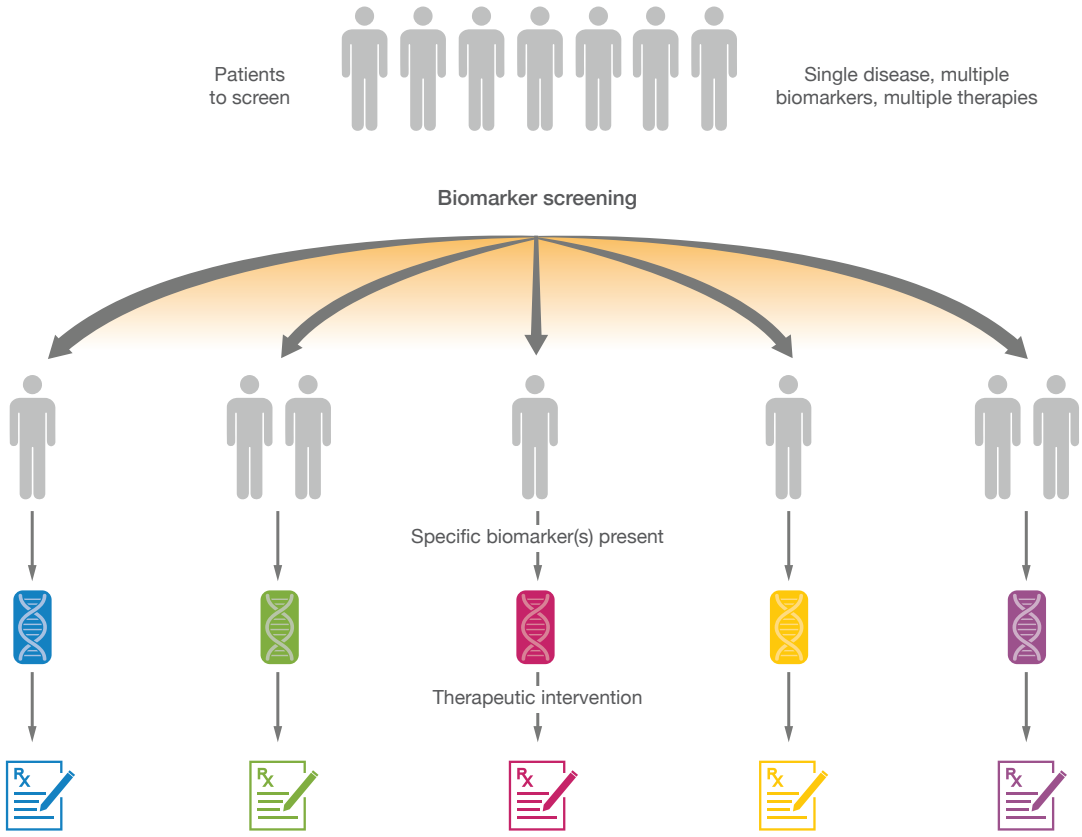
Molecular matching of a patient's cancer with an approved or investigational therapy is essential for increasing the chances of achieving better clinical outcomes. Multiple studies have shown that genomically matching patients to targeted therapies or immunotherapies results in improved clinical outcomes.[10-15]

- Increased overall response
- Increased disease control
- Extended progression-free survival (PFS)
- Longer overall survival (OS)
- Reduced treatment-related adverse effects (AE)

CGP enables more patients to be matched to approved or investigational therapies.[6,10,45,47,48] Additionally, CGP can improve patient enrollment in genomically matched clinical trials.[10,47]

> "Use of NGS panels in clinical practice may help to choose the best therapeutic options for the patients with actionable alterations."
>
> **Dr. Bernard Doger de Spéville**
> Medical Oncologist,
> Fundación Jiménez Díaz

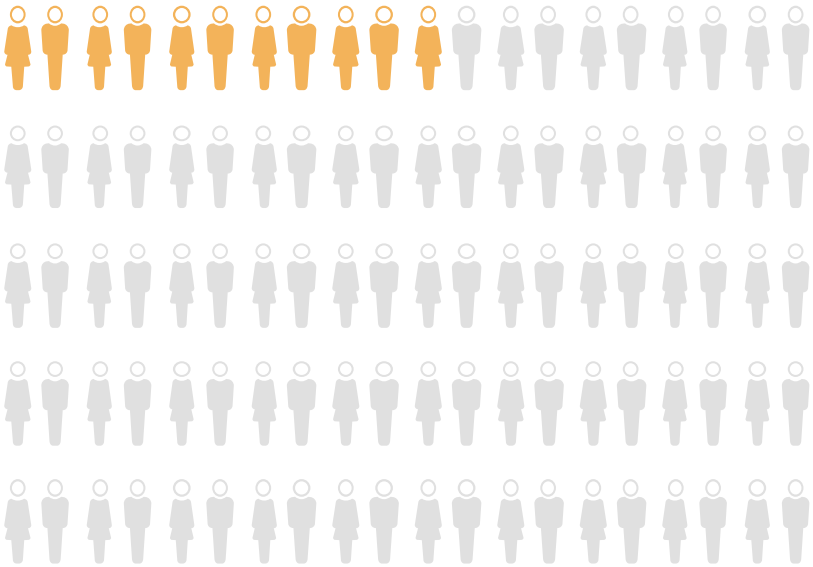
Patients are assigned a molecular therapy or eligibility for a clinical trial based on the tumor molecular profile



Matched therapy can lead to better patient outcomes

Study and description	Outcome	Reference
A retrospective review of 814 patients with NSCLC	OS for patients receiving molecularly targeted therapy: **31.8 months; 95% CI** OS for patients receiving chemotherapy: **12.7 months; 95% CI**	Gutierrez ME, et al[12]
A study of ~1700 patients with advanced NSCLC	OS for patients receiving molecularly matched therapy: **18.6 months**; 95% CI OS for patients receiving nontargeted therapy: **11.4 months**; 95% CI	Singal G, et al[13]
A study of 101 patients with lung adenocarcinoma who had CGP performed	Influenced treatment decision in **~50% of cases** **ORR: 65%**	Rozenblum AB, et al[15]
A study of 429 cancer patients; 62% received matched therapies	**Longer PFS**: Hazard ratio (HR) = 0.63; 95% CI, 0.50–0.80; P < 0.001 **Longer OS**: HR = 0.67; 95% CI, 0.50–0.90; P = 0.007 **Higher stable disease**: ≥ 6 months/partial/complete remission rate (52.1% vs 30.4% P < 0.001 nonmatched therapy)	Kato S, et al[14]
A study of 149 patients with stage IV metastatic cancers; 49% received matched therapies	**Longer PFS**: median 6.5 vs. 3.1 months; P = 0.001; HR = 0.34; 95% CI, 0.19-0.62 **Longer OS**: HR = 0.42; 95% CI, 0.18-0.95	Sicklick JK, et al[63]

CGP can have a positive impact on patient enrollment in genomically matched clinical trials[10,47]



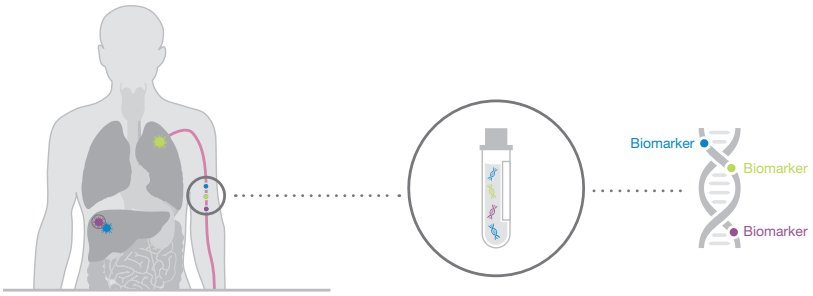
11%

Rate of patients eligible to enroll in a clinical trial based on CGP test results, according to prospective study with 10,000 patients.[10]

Adding CGP from liquid biopsy further enables precision medicine

Circulating tumor DNA (ctDNA) in the blood can act as source material for CGP tests[64] and provide results that inform subsequent therapy selection[65,66], including immunotherapy.[67,68]

ctDNA is obtained using a simple blood draw



DNA from tumors circulates in the blood

Cell-free DNA is extracted from plasma

Liquid biopsy is recommended today by guidelines

Different tumor types may have specific use cases for liquid biopsy, such as when:

- Patient is medically unfit for a tissue biopsy
- Insufficient material is available (QNS)
- Tissue biopsy is unavailable

Immuno-oncology biomarkers

CGP tests using liquid biopsy can detect genetic signatures, such as MSI and TMB:

MSI measured by CGP from blood (ctDNA) has been observed to be highly concordant with tissue-based standard-of-care testing with similar clinical utility for advanced gastric cancer patients on immunotherapy treatment.[67]

TMB measured from blood (bTMB) using CGP has been associated with improved clinical outcomes when ≥ 20 mutations per megabase were detected in mNSCLC.[68-72]

Liquid biopsy is complementary to tissue

+15%

more clinically relevant mutations identified in mNSCLC when analysis from liquid biopsy is added to tissue[73-75]

Liquid biopsy for insufficient tissue quality or quantity

~20%

of the time clinical NGS is prevented from FFPE samples in advanced cancers[73,76,77]

Clinical trials benefit from liquid biopsy

↓3x

decrease in screening time

↑2.3x

increase in enrollment rate in advanced gastrointestinal cancer compared to CGP from tissue only[78]

Patient impact

Case study: More than typical back pain

An 11-year-old girl started experiencing severe back pain that was not relieved using over-the-counter medications. Upon further exploration, doctors discovered that she had a tumor wrapped around her aorta and spine.[79] Doctors operated and removed the tumor, but the cancer returned. Chemotherapy was unsuccessful. The tumors grew and the pain continued.[80]

Looking for answers, doctors ordered a CGP test that combined DNA and RNA sequencing.[79,81] CGP identified a novel *STRN-NTRK2* fusion.[79] *NTRK* fusions are extremely rare, occurring in < 1% of solid tumors.[82] Knowing an underlying oncogenic driver of her cancer, doctors were able to enroll the girl in a clinical trial for larotrectinib.[83] With treatment, the tumors have disappeared and the girl no longer experiences back pain.[80]

CGP identifies prevalent and rare biomarkers in a single test, maximizing the ability to identify one that is actionable.

Case study: A new standard of care for cervical carcinosarcoma

A 58-year-old woman who had previously been treated for metastatic cervical carcinosarcoma presented at the treating clinic with pain. Cervical carcinosarcomas occur in < 1% of women with invasive cervical neoplasms,[84] and therefore have not been thoroughly characterized.[85] Her initial diagnosis was treated with a combination of radiation therapies and chemotherapies. In three years, there had been no evidence of recurrence.[85]

At this new visit, cancer serum biomarkers, other than human epididymis protein 4 (HE4), appeared normal. Cryosurgery was performed, during which tumor and plasma samples were obtained. These samples were subject to TMB and MSI evaluation using NGS-based mutation profiling. The results identified > 500 somatic mutations and an extremely high TMB. Targeted therapies were not available for the identified mutations; the patient was administered cryoablation followed by pembrolizumab based on the high TMB. At the time of submission of the Zhu et al manuscript, the patient had a PFS of 11 months.[85]

High TMB influenced patient treatment regimen.

Realizing the promise of precision medicine

Not all cancers harbor the same variants. To add more complexity, the same variants can drive different cancer types. Just as there is not one cause, there is not one therapy. The more that is learned about the underlying genetics of a tumor, the more it becomes clear that each patient needs an individualized approach to treatment. This is precision medicine. Providing care for each patient based on the tumor's genomic makeup.

The continuous discovery of biomarkers and rampant pace of new therapy development bring us closer to achieving this goal every day. To keep pace, appropriate tests are needed. A significant change in the way cancer is characterized is imperative. We need tests that provide sensitive, accurate results quickly using minimal sample input. Actionable results that relate to therapeutic options, including clinical trials. CGP delivers this shift. A single CGP test using minimal sample can assess multiple DNA and RNA variant types across hundreds of genes. Sophisticated analytics interpret these results and produce easy-to-interpret reports that include recommended therapies and clinical trials. Using CGP, improving patient outcomes moves from a possibility to a reality.[10-15]

CGP. One sample. One test. One report. More opportunities.

"In the future [we need] to move from this fragmented landscape of biomarkers to a situation where, at least in Stage 4 [cancer], we do comprehensive profiling for each and every patient."

Prof. Dr. Wilko Weichert
Pathology, Technical University Munich

A change in paradigm

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