Quest Advanced®

Identifying Genetic Drivers of Solid Tumors:

A paradigm shift in diagnostics and patient treatment

The diagnosis and treatment journey for people with solid tumors changed significantly over the past 25 years. It started with the recognition of cancer as a genetic disorder. This revolutionary characterization of cancer has advanced both treatments and diagnostics. Essentially, each change in treatment, each newly discovered biomarker, has required a transformation in diagnostics.

For example, in 1998, trastuzumab, a monoclonal antibody used to treat metastatic breast cancer characterized by *HER2* overexpression, along with a diagnostic assay to detect *HER2*, received FDA approval. This was the **"first targeted cancer drug to use the drug-diagnostic co-development model."**[1]

Twenty-five years forward, robust diagnostic capacity and flexibility that provide oncologists, pathologists, and lab directors the complete genomic picture of solid tumors, is essential for treatment decision-making. Comprehensive genomic profiling (CGP) that aligns patient care with current treatments, clinical trials, and emerging therapies—all specific to biomarkers —makes real the promise of precision medicine to drive better outcomes.

How we got here:

Moving from chemotherapy to immunotherapy

The paradigm shift of cancer as a genetic disorder led to further understanding of the altered proteins, disrupted biochemical pathways, and the disarrangement of the normal functioning of cancer cells in their microenvironment.

Scientists worked to consider how cancers interrupt the normal activity of the immune system. One advancement was the identification of *CTLA-4* as a protein that puts the "brakes" on the immune system. From there, James Allison's Nobel prize-winning work developed an antibody to *CTLA-4* that allows T cells to persist in killing cancer tumor cells.[2] FDA approval of anti – *CTLA-4* checkpoint blockade therapy (ipilimumab) to treat metastatic melanoma in 2011 was hailed as a "therapeutic breakthrough in cancer immunotherapy."[3]

Another Nobel recipient, Tasuku Honjo, worked on the *PD-1* protein found on T cells and *PD-L1* found in higher than normal amounts on some cancer cells. He developed a blockade human anti – *PD-1* antibody named nivolumab and by 2018 over a dozen tumors had been approved for treatment with *PD-1* blockade therapy. FDA approval has been given for nivolumab use in all microsatellite instability-high (MSI-H) cancers, no matter origin of their tumors.[4] As Honjo stated in his Nobel acceptance, "Clearly, *PD-1* blockade treatment has brought a paradigm shift in cancer therapy due to its efficacy over a wide range of tumors; durability of its effects in those who respond; and importantly…few adverse effects compared with previous treatments."[4]

New research techniques lead to new therapies

In 2022, the FDA issued 28 regular approvals, 9 accelerated approvals, and 2 conversions from accelerated to full approvals, primarily for solid tumors.[5]

Innovative research techniques contributed to these approvals. For instance, the hit-to-lead process employing high-throughput screening identified a small molecule for the "undruggable" *KRAS* mutation. *KRAS* is mutated in 22% of all cancer patients, including pancreatic cancers (61%), colon cancer (33%), and lung cancer (17%).[6] Two medications approved recently, sotorasib (Lumakras™) and adagrasib (Krazati®), target the *KRAS* G12C mutation. This success stimulated research on other "undruggable" targets like the tumor suppressor p53. Treatments to restabilize p53 proteins with the Y220C mutation are underway.[7]

Another innovative treatment, neoadjuvant therapy with an immune checkpoint inhibitor, resulted in a complete clinical response in one solid tumor clinical trial. The *New England Journal of Medicine* reported that 12 patients with locally advanced rectal cancer were treated with dostarlimab before any other treatment—no surgery or chemoradiotherapy. All 12 patients showed no evidence of tumor during a 5- to 25-month follow-up.[8]

Genomic markers driving precision medicine

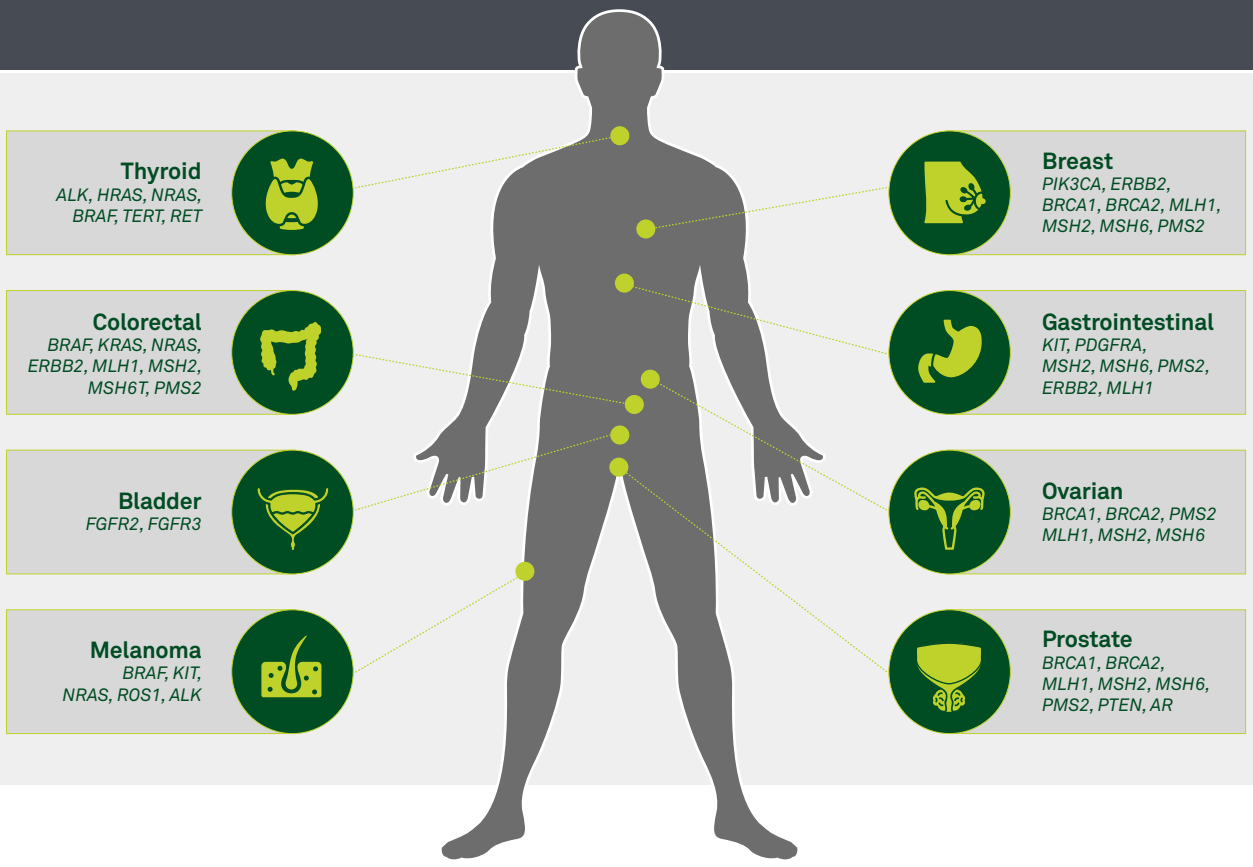
This fundamental change in cancer treatment means that precision medicine—targeting the genomic changes in cancer cells—is now the norm. Formerly defined by anatomical location, genomic markers (biomarkers) now describe solid tumors and inform their treatment, making precision medicine available for all solid tumors of any tissue type at any point in the treatment journey. Since the location of the cancer does not matter in the same way that treatment and biomarkers do, these tumor-agnostic (also called tissue-agnostic) therapies (microsatellite instability, tumor mutational burden, and *NTRK* fusions) all require new diagnostic tools.[9]

Clinical benefit from one or a combination of precision medicine therapies, in many different cancer types—melanoma, gastric, or lung, for example—is now achievable.

The rapidly evolving influx of targeted therapies, diagnostic approvals, and clinical trials could understandably challenge and exceed the time and energy capacity of many physicians and health systems.[10-13] **Comprehensive Genomic Profiling (CGP) provides the detailed information to facilitate treatment decision-making.**

Biomarkers in US guidelines and drug labels for highly prevalent tumors[14-16]

Solid tumors (pan-cancer): *NTRK*, TMB, MSI



Comprehensive Genomic Profiling:
One test fills many needs

Advances in standards of care point to the need for a broad oncology diagnostic tool: Comprehensive Genomic Profiling (CGP).

CGP is a next-generation sequencing (NGS) tool offering a more streamlined option for testing multiple biomarkers at one time. In this way, CGP can reduce the complexity and fragmentation that could negatively impact treatment and caregiving.

One test conserves biopsy tissue

In just one test, an expanded CGP panel detects information across hundreds of genes. Assessing both rare and prevalent biomarkers with just one biopsy sample increases the chances of finding cellular changes that are treatable for thyroid, colorectal, bladder, melanoma, breast, gastrointestinal, ovarian, and prostate solid tumor cancers.

One test finds many treatable alterations quickly

By assessing all biomarkers at once, CGP finds more actionable and treatable alterations and molecular signatures. CGP allows for multiple biomarkers to be tested at once, which can reduce the amounts of sample required and potentially provide faster results.

One test identifies RNA fusions

Juxtaposing 2 different genes during chromosomal rearrangement can result in fusion genes. Fusion genes play a significant role in tumorigenesis, yet rapid and accurate identification of fusions has been challenging and often limited to testing for only one fusion gene at a time.

Next-generation sequencing CGP provides in-depth analysis with broad genomic coverage. For example, in one study of 3,218 advanced solid tumors diagnosed over a 2-year period (2019-2021), NGS CGP found that 217 (6.7%) harbored RNA fusions. Of those, 64 (29%) were actionable, matching targeted therapies, and 69 (31%) matched one or more basket clinical trials.[17]

Using NGS CGP gives patients who otherwise might not have an available treatment the opportunity to obtain targeted therapy through approved precision medicine or available clinical trials.

One test compared to single-gene and small hotspot panel testing

Research shows the limitations of single-gene and small hotspot panels. In one prospective study involving 10,000 patients with refractory cancer, small hotspot panel testing missed 81% of actionable mutations.[18]

In terms of identification differences, in one study of NSCLC, colorectal cancer (CRC), and melanoma solid tumors, NGS identified additional targetable alterations in 44% of the NSCLC tumors, 22% of the CRC, and 14% of the melanomas.[19]

Likewise, in a study of 521 patients with solid tumors who were tested with a hotspot assay and a CGP assay, 214 (41%) had at least one actionable gene alteration that had not been identified in the hotspot assay. Of those 214 patients, 19% underwent matched therapy and had significantly improved overall survival compared with those treated with unmatched therapy.[20]

One test identifies many molecular signatures

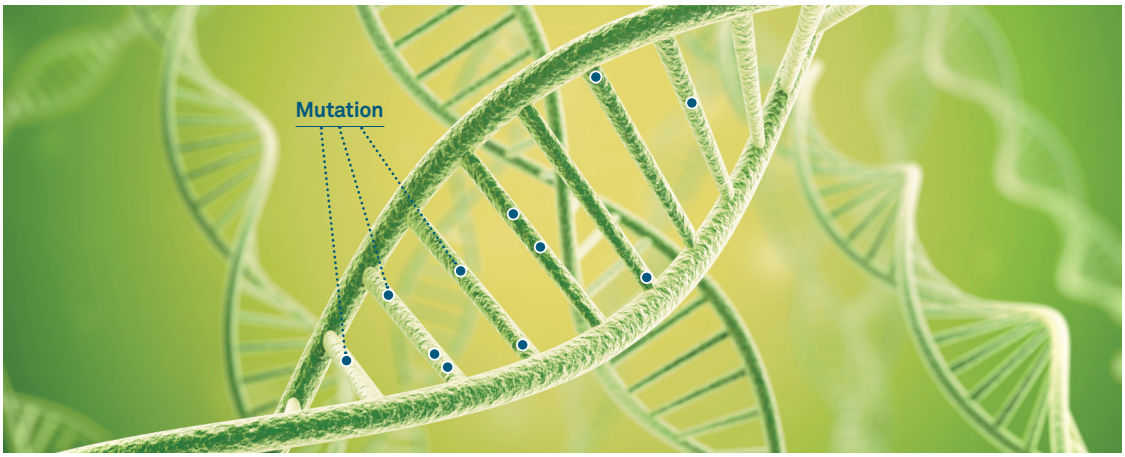
Unlike smaller assays, CGP delivers information on 2 FDA-approved biomarkers that both the National Comprehensive Cancer Network® (NCCN®) and the European Society for Medical Oncology (ESMO) recommend testing for tumor mutational burden (TMB) and microsatellite instability (MSI).[21,22]

Tumor Mutational Burden (TMB)

TMB "…is a numeric index that expresses the number of mutations per megabase (muts/Mb) harbored by tumor cells…."[23] High TMB is defined as having greater than or equal to 10 muts/Mb. Across tumor types and tissues, studies have found between 10% and 26% with high TMB.[24-26]

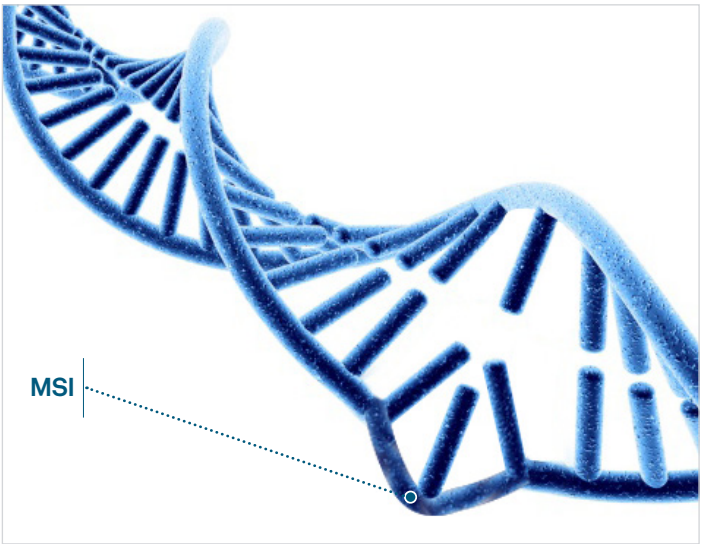
The Phase II Keynote-158 study using pembrolizumab monotherapy on recurrent or metastatic solid tumors across multiple tissues found that those with TMB ≥175 mutations/exome treated with immunotherapy showed clinical improvement and improved outcomes versus chemotherapy.[27]

High-TMB has been described as a "predictive biomarker, potentially indicating a high rate of response to immunotherapy."[23]



Microsatellite Instability (MSI)

The National Cancer Institute defines MSI as "[A] change that occurs in certain cells (such as cancer cells) in which the number of repeated DNA bases in a microsatellite (a short, repeated sequence of DNA) is different from what it was when the microsatellite was inherited." A change rate of 30% or more is considered MSI-High (MSI-H).[28] The FDA has approved MSI-H status as a threshold to treat solid tumors with checkpoint inhibitors.



Research on **patient outcomes when using CGP**

One study compared the degree of matching tumor biomarkers to treatment on outcomes for patients. Patients with gynecological and breast cancer solid tumors underwent CGP. A matching score looked at the percentage of biomarkers targeted by treatment over total pathogenic alterations. Those patients whose tumors had a matching score greater than 40% had higher overall response rates and progression-free survival.[29]

In another study, patients with colorectal cancer had next-generation CGP for a targeted clinical trial. Median overall survival was significantly longer for patients receiving the targeted treatment instead of standard treatment.[30]

Aligns with standard of care

In 2018, Medicare and Medicaid confirmed the need for next-generation comprehensive testing for Medicare recipients in their National Coverage Policy Document.[31] Among other cancers, NCCN guidelines recommend NGS for cancers of the breast, central nervous system, colon and rectum, esophagus and esophagogastric junction, gastric, gastrointestinal stromal, melanoma, NSCLC, ovarian, pancreatic, prostate, small bowel, soft tissue, and thyroid.[32,33]

Identifies potential eligibility for matched clinical trials

CGP data can determine patients' eligibility for clinical trials. Many trials now assign treatments based on molecular profiles of tumors rather than histology. For example, the Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) clinical trial (NCT0458945) is a Phase II trial for patients with solid tumors. The participants "...will be treated with a drug or drug regimen tailored to their NGS assay results at screening. Participants will be assigned to the appropriate cohort based on their genetic alteration. Treatments will be assigned on the basis of relevant oncogenotype..."[34]

Navigates constantly emerging therapies beyond the current standard of care

With CGP, the physician receives the most up-to-date information about their patient's solid tumor(s). The right laboratory will also provide information about matching treatments—both those approved and those in clinical trials—that enable precision treatment to begin as soon as possible.

NSCLC patient journey: individual single gene tests or multi-gene panels compared to CGP[35-40]

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 based on an NSCLC patient. Test times and tissue requirements for the NSCLC example complied from test menus offered by various medical laboratories.

8 important requirements for a CGP solid tumor diagnostic laboratory

It is important to note that not all laboratories provide the same CGP.
Choose a solid tumor diagnostic laboratory that offers the following:

Broad test menu

A CGP solid tumor diagnostic laboratory that provides robust and flexible testing for over 500 genes. The laboratory must have the capacity to perform NGS for MSI and TMB.

Clear, concise reports

Reports that are understandable and present FDA-cleared, guideline-based treatment options that match actionable molecular targets. The reports should describe emerging genes and provide clear guidance for possible treatment options.

Optimized turnaround time

Rapid turnaround that can deliver a report within 14 days

Clinical trial information

Detailed intelligence on potential clinical trials that can be pursued to provide as many options as possible for patients.

Access to experts

Professional consultation with laboratory oncologists and pathologists to assist practitioners in decision-making based on laboratory results. These experts should be able to connect patients and physicians with clinical trial sponsors and clinical research organizations. There should be an easily accessed toll-free number for timely consultations.

Comprehensive health plan access

In-network status with most health plans, including Medicare and private payers. Patient financial assistance programs should be part of the laboratory's offerings.

Block retrieval services

Since CGP uses less tissue and conserves the sample, your lab must have up-to-date, digitally stored intelligence on all available and emerging treatments. When a sample is not available, it is important to have a laboratory that offers biopsy sample retrieval services.

Capability to interact with your EHR system

Your lab should help you work more effectively by simplifying the workflow, whether you are ordering tests, arranging for expert consultation, or investigating treatment options.

Precision medicine's promise **made possible**

Solid tumor treatment guided only by histology and tumor location is quickly becoming part of the past. Understanding the genetic nature of cancer and the drivers of unrestricted cell growth allows for new treatments and new diagnostic tools. Precision medicine targeting genomic changes in cancer cells is the new norm.

This paradigm shift in our understanding has led to tumor-agnostic treatments requiring new diagnostic tools that can identify biomarkers, but the momentum of change and research advances are taxing the time and reserves of many physicians and health systems.

Benefits of using a comprehensive diagnostic laboratory with state-of-the-art solid tumor CGP include:

1. Linking genetic findings with current standards of care
2. Helping physicians navigate emerging treatments
3. Saving time and conserving biopsy samples
4. Easing the burden on healthcare providers by providing information on clinical trials

Quest Advanced® Oncology offers CGP with a comprehensive menu of solid tumor solutions to help clinicians find the best treatment plan and care for patients with solid tumors

Visit QuestDiagnostics.com/SolidTumor to learn more about how we can keep you at the forefront of rapid advancements in cancer care.

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