

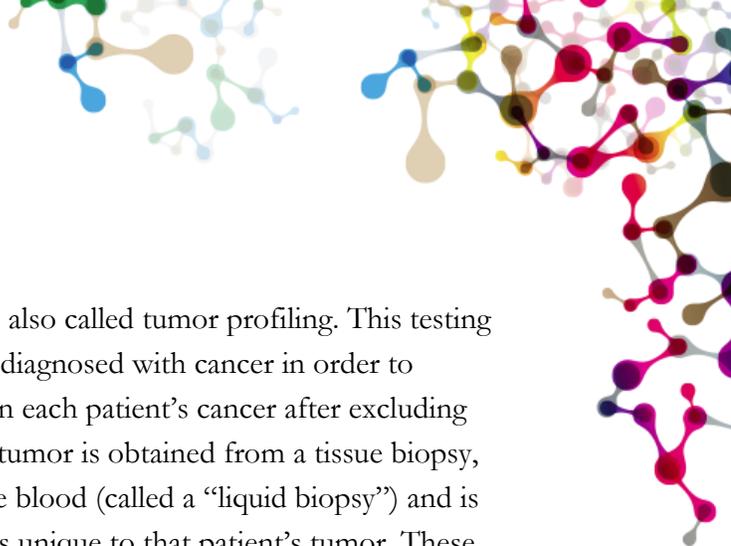


# Use of Genetic Testing in Oncology to Improve Clinical Outcomes in Preventative Care and Personalized Medicine

New discoveries in DNA sequencing and cancer research have resulted in the rapid development of sophisticated and accurate genetic testing. Genetic testing and diagnostics have enabled an unprecedented degree of personalization in cancer therapies while potentially relieving patients from the unpleasant side effects of cytotoxic chemotherapies. Despite the high-tech, cutting-edge nature of next-generation cancer screenings and diagnostics, their affordability, coverage by health insurance, and turnaround times continue to improve. These and other emerging technologies represent the bright future of improved access to preventative care and personalized medicine. Below is a guide to how the latest in testing options can be utilized to improve clinical outcomes in cancer prevention and personalized cancer treatment.

## Germline/Hereditary Testing

Oncology genetic tests fall into two main categories: germline testing and somatic testing. Germline testing, i.e., sequencing of the patient's genomic DNA, is often performed on a blood or saliva sample. Germline tests determine the DNA sequence of the patient's genome: the 3 billion nucleotides contributed from their mother and father. Through our rapidly growing knowledge of the DNA sequence of the human genome and our understanding of how inherited genetic changes can result in predispositions to various forms of cancer, hereditary testing can predict a patient's relative future risk of developing cancer and other diseases. Germline testing is particularly indicated for people who are cancer free but who have a blood relative with hereditary cancer to determine if they carry the same genetic predisposition. In consultation with a patient's physician, these genetic cancer predisposition findings are invaluable for determining appropriate medical management and intervention strategies that can mitigate future cancer risk. **Hereditary tests are important for patients already diagnosed with cancer, as the results can expose crucial information about the specific, most effective treatments available, the patient's risk of cancer recurrence, and the risk of the patient's blood relatives developing cancer.**

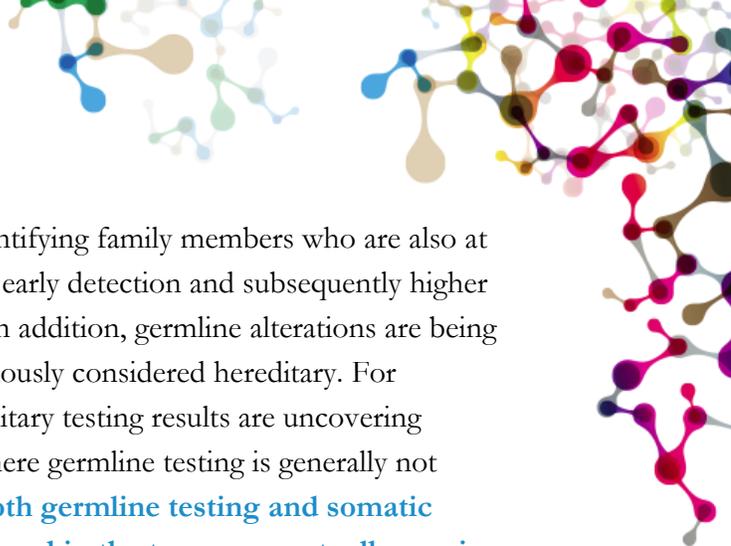


## Somatic Testing/Tumor Profiling

The second category of genetic tests is somatic testing, also called tumor profiling. This testing is done exclusively for patients who have already been diagnosed with cancer in order to determine the genetic mutations specific to the DNA in each patient's cancer after excluding germline findings. In these cases, cancer DNA from a tumor is obtained from a tissue biopsy, surgical sample, or plasma sample acquired from whole blood (called a "liquid biopsy") and is then analyzed to identify the DNA sequence alterations unique to that patient's tumor. These tests often assess a broad panel of "biomarkers" comprised of specific sequences in genes associated with malignancy, metastasis, risk of recurrence, and responsiveness to various targeted cancer therapies. These changes can be large scale, comprising major truncations of gene sequences or even involve translocations of chunks of DNA from one gene to another, or they may change only a single base pair, in which case they may be termed single nucleotide variations (SNVs). Identifying such genomic aberrations in the patient's tumor can guide physicians regarding treatment options, as these sequence changes can be predictors of response or resistance to certain therapies. Upon evidence in the medical literature of such behavior, these sequence alterations are called actionable aberrations. New biomarkers are being discovered at a rapid pace—almost daily—resulting in ever-expanding testing panels and knowledge of the utility of biomarkers in cancer treatment. Furthermore, insurance companies are increasingly providing reimbursement to patients for such tests because of the growing acceptance of their usefulness by medical practitioners. For example, **Medicare now reimburses somatic testing for stage III and IV cancer patients as a standard practice.<sup>1</sup> In summary, somatic testing results can be critical before or during the decision-making process when the patient and his/her physician are determining a treatment plan.**

## The Importance and Significance of Performing Both Types of Genetic Tests

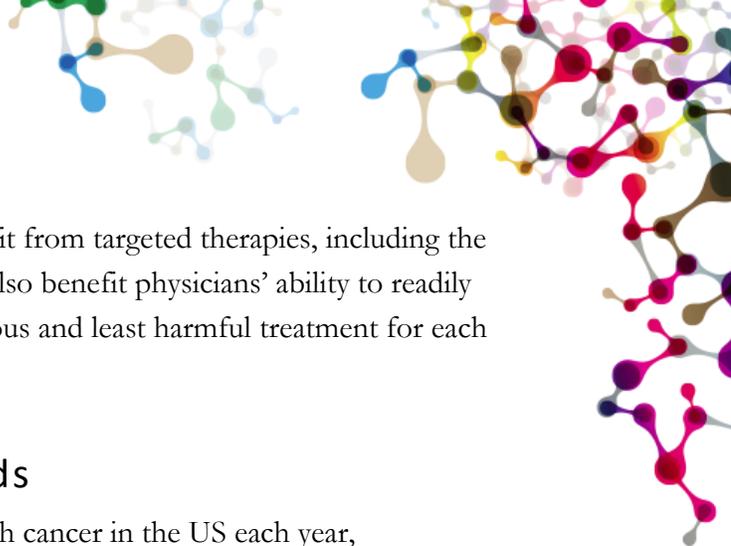
Knowledge of both the germline and somatic DNA sequences for a given patient is important to enable the identification of an effective and individually tailored treatment plan. For example, cancer patients with germline findings may be associated with a higher risk of recurrence.<sup>2</sup> Moreover, comparative analysis of the two sequence sets, so-called paired tumor-normal analysis, can provide additional insights based on determining whether DNA aberrations existing in the patient's tumor tissue are also found in the patient's germline (therefore, they are not truly somatic).<sup>3</sup> In this way, concurrent tumor and germline profiling can help to personalize a treatment plan for the patient and also identify family members of that patient who are at



increased risk for developing cancer in the future.<sup>4</sup> Identifying family members who are also at risk can assist in preventative care as well as leading to early detection and subsequently higher cure rates should those relatives also develop cancer. In addition, germline alterations are being found in patients with cancer types that were not previously considered hereditary. For example, prudent paired analyses of somatic and hereditary testing results are uncovering germline findings on a consistent basis and in cases where germline testing is generally not considered.<sup>5</sup> Therefore, **it is important to perform both germline testing and somatic testing to know whether or not DNA alterations found in the tumor are actually coming from the patient's germline DNA, as this status can influence treatment or prevention decisions made by the patient and their physician.**

## A Multitude of Evolving Options for Genetic Testing

The genetic testing market has grown dramatically over the past several years. There are now literally thousands of tests available. However, the large number of available options and the complexity of the related technology and terminology can be bewildering and overwhelming for patients and even care providers. Somatic testing in particular constitutes cutting-edge science, revealing new information that contributes to the development of new commercially available tests on a regular basis. These tests can be instrumental in accurately predicting and determining a patient's potential response to a growing menu of targeted therapies, such as the promising area of immuno-oncology. In companion diagnostics, for example, testing for specific aberrations is required for the use of certain therapies as approved by the FDA. Treatment with the Programmed Death-Ligand 1 (PD-L1) checkpoint inhibitor **Keytruda (pembrolizumab), approved in 2017 for all tumor types,**<sup>6</sup> is contingent upon results from the use of companion diagnostics that test for PD-L1 expression<sup>7</sup> and for MicroSatellite Instability/MisMatch Repair (MSI/MMR) status. Patients can test positive or negative for PD-L1 expression on the tumor cell surface with varying clinical significance depending on the type of cancer involved.<sup>8</sup> MSI creates a predisposition to the occurrence of somatic DNA alterations in genes that can contribute to cancer progression. Consequently, patients with MSI may benefit from treatment with Keytruda. Tumor Mutational Burden (TMB) is also becoming a significant biomarker for immunotherapy. TMB measures the number of aberrant sequences found in the tumor DNA.<sup>9</sup> **The FDA approved the first commercially available broad panel genomic assay as a companion diagnostic for 17 targeted therapies in December 2017.**<sup>10</sup> In addition, complementary diagnostic tests may inform a patient and their physician about an entire class of treatments, such as the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in patients with wild type (non-aberrant) KRAS genes.<sup>11</sup> Specific molecular profiling offered through germline and somatic testing has substantially enhanced our understanding of



the degree to which a patient can be expected to benefit from targeted therapies, including the most advanced cancer treatments. Such profiling can also benefit physicians' ability to readily identify, among a myriad of options, the most efficacious and least harmful treatment for each individual.

## Current Situation and Unmet Needs

Of the approximately 1.7 million people diagnosed with cancer in the US each year, approximately half are diagnosed in Stage III or IV, a key population for somatic testing. However, a majority of these cancer patients do not receive any genetic testing or access to experts in genetics.<sup>12,13</sup> Unfortunately, current published testing guidelines lag behind the latest developments, and thus these guidelines don't always represent the current best options available in this area of patient care. Guidelines for germline testing and the interpretation of test results are still relatively underutilized as standard practice in oncology. Furthermore, guidelines for somatic testing and the interpretation of those results are virtually non-existent, due to its newness and rapidly changing nature. Because of the speed of development and its inherent complexity, training in genetic testing and specialization in the technology is mandatory for staying abreast of advances in this constantly evolving area. To provide the best patient care it is imperative to utilize experts in genetics capable of navigating current testing options and identifying which tests might be most appropriate for a patient's pathology and medical history. As the field continues to advance, **genetic testing outcomes are correlating increasingly with existing approved targeted therapies and/or ongoing clinical trials, i.e., therapy/trials matched to genomic results.** Therefore, employing medical professionals with up-to-date expertise in genetic testing can enhance a patient's prospects for improved short-term or long-term survival.

Telegenetics, i.e., genetic testing expertise provided over the phone (or via video conferencing), may play a valuable role in supporting providers and patients remotely. **A telegenetics clinic with expertise in the interpretation of somatic and germline testing data in terms of clinical significance and potential treatment options can assess patients from both testing perspectives while fulfilling the above-mentioned unmet needs.** Personalized medicine is giving patients opportunities for improved clinical outcomes and, in some cases, leading to cures. This trend is expected to continue with the expansion of useful biomarkers, the development of diagnostic tests based on those biomarkers, and advances in targeted therapies, including immunotherapies, that are indicated by test results.

## The Considerable Advantages of Telegenetics

Although telegenetics is widely accepted as safe and effective, waiting lists for initial in-person appointments are often long—a legitimate concern for patients whose cancer is progressing. Telegenetics is cost-effective compared with in-person counseling and reduces a patient’s time away from work or home in traveling to and preparing for in-person visits. Telegenetics can also be used to connect urban specialists with distant patients (or distant family members) and their local doctor to create continuity of care. Access to cancer genetics experts, including MD or PhD geneticists and/or board-certified Genetic Counselors, can be challenging for patients and providers, especially those who reside outside of large urban treatment centers. A large proportion of cancer genetics experts are concentrated in big cities where they are affiliated with major research medical centers or universities. Over half of the approximately 15 million people with cancer in the US are treated through a local community cancer center. Due to resource limitations and an absence of research activity in emerging technologies, the medical staff of community cancer centers in rural areas might not have ready access to cancer genetics experts. Fortunately, telegenetics lends itself well to the practice of telemedicine. **By virtue of telemedicine, all patients can receive medical guidance for their disease, regardless of their geographic location. A telegenetics clinic does not replace a patient’s oncology team. Rather, a cancer telegenetics clinic can supplement the oncology team with a wealth of expertise in cancer genetics that traditional oncology teams may lack. A telegenetics clinic can recommend tests, interpret and discuss test results, answer technical questions, and provide the patient’s oncology team with a clinical report including informed, individualized recommendations based on genetic test results.** This clinical report is especially valuable to the oncology team, because test results may require in-depth genetics knowledge and expertise for accurate interpretation. The analysis performed by the telegenetics clinic may also uncover new treatment options, potential clinical trials in which to enroll, or germline findings that can shed light not only on the potential effectiveness of various treatments and preventative options, but also the disease susceptibility of a patient’s family members.

## Conclusion

In summary, employing cancer genetic expertise not only improves a patient’s access to both somatic and germline testing, but can also better inform the oncology team about personalizing a treatment plan and/or expanding the reach of preventative care. Just as patients consider the relative expertise of the other members of their healthcare team, they understandably seek the most competent telegenetics clinic specializing in cancer genetics from this limited pool of experts. To make the most effective use of the available genetic testing options, patients and

their healthcare providers will greatly benefit from a cancer telegenetics clinic with expertise and a well-integrated approach to cancer testing. **The ideal telegenetics clinic will have dual expertise in both germline and somatic testing and interpretation to contribute to improving clinical outcomes by providing effective service delivery to patients, their families, and the caregivers who support them.**



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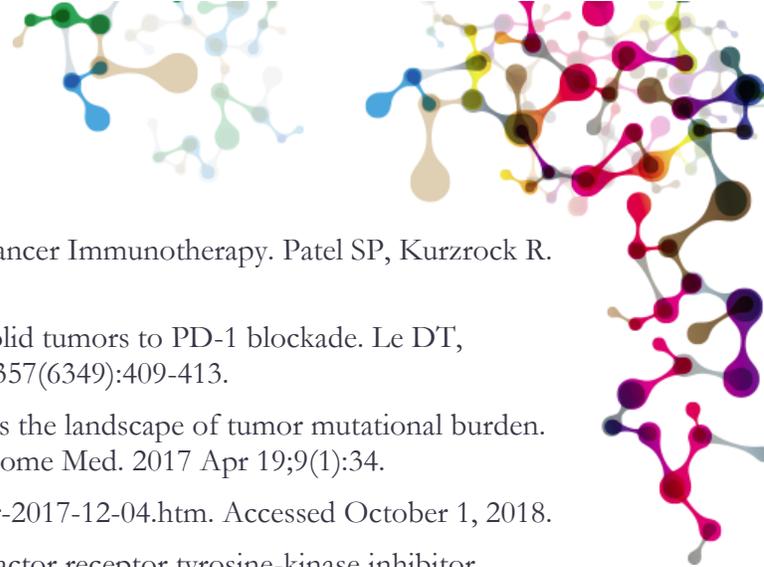


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## References

1. <https://www.medscape.com/viewarticle/894190>. Accessed October 1, 2018.
2. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. Castro E, Goh C, Olmos D, et al. *J Clin Oncol*. 2013 May 10; 31(14):1748-57.
3. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. Mandelker D, Zhang L, Kemel Y, et al. *JAMA*. 2017 Sep 5; 318(9):825-835.
4. The right drugs at the right time for the right patient: the MD Anderson precision oncology decision support platform. Johnson A, Zeng J, Bailey AM, et al. *Drug Discov Today*. 2015 Dec; 20(12):1433-8.
5. Additional germline findings from a tumor profiling program. Stjepanovic N, Stockley TL, Bedard PL, et al. *BMC Med Genomics*. 2018 Aug 9; 11(1):65.
6. <https://www.cancer.org/latest-news/fda-approves-keytruda-pembrolizumab-for-any-tumor-with-specific-genetic-change.html>. Accessed October 1, 2018.

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7. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. Patel SP, Kurzrock R. *Mol Cancer Ther*. 2015 Apr; 14(4):847-56.
  8. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Le DT, Durham JN, Smith KN, et al. *Science*. 2017 Jul 28; 357(6349):409-413.
  9. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Chalmers ZR, Connelly CF, Fabrizio D, et al. *Genome Med*. 2017 Apr 19;9(1):34.
  10. <https://www.roche.com/media/releases/med-cor-2017-12-04.htm>. Accessed October 1, 2018.
  11. KRAS status and resistance to epidermal growth factor receptor tyrosine-kinase inhibitor treatment in patients with metastatic colorectal cancer: a meta-analysis. Li W1, Shi Q, Wang W, et al. *Colorectal Dis*. 2014 Nov; 16(11):O370-8.
  12. National estimates of genetic testing in women with a history of breast or ovarian cancer. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. *J Clin Oncol*. 2017 Dec 1; 35(34):3800-3806.
  13. Underutilization and disparities in access to EGFR testing among Medicare patients with lung cancer from 2010 - 2013. Lynch JA, Berse B, Rabb M, et al. *BMC Cancer*. 2018 Mar 20;18(1):306.