
The Value of Molecular Diagnostics:

Advancing Cancer Treatment and Care



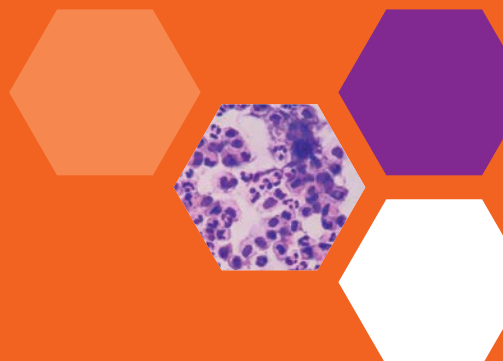
AdvaMedDx
Vital Insights | Transforming Care

The introduction and expanding use of molecular diagnostic tests to detect cancer and manage cancer care mark a major milestone and herald future progress in the fight against this disease. This brief report is intended to concisely summarize the complex science underlying the use of molecular diagnostics, particularly genetic tests, and their application in cancer screening, diagnosis, prognosis, treatment selection, and monitoring.

Cancer is a major public health challenge. In 2016, more than 1.7 million people in the U.S. are expected to receive a cancer diagnosis in the United States.¹ The number of new cancer cases per year is expected to be almost 2.4 million in the U.S., and 24 million globally, by 2035.²

A combination of better prevention, earlier detection, increased public awareness, improved diagnosis, and more advanced therapies are driving progress in the fight against cancer. Since 1971, the percentage of the US population living with or after a cancer diagnosis has more than tripled.² Molecular diagnostic technologies are now emerging as a key contributor to reducing the burden of cancer in the future.

Diagnostic tests are at the forefront of medical innovation, providing vital insights into patient health and transforming cancer care. Diagnostics provide critical insights at every stage of cancer care — prevention, detection, diagnosis, treatment and successful management. With the potential to fundamentally change clinical practice, these technologies are intended to match the right patient with the right treatment at the right time.³



Molecular Diagnostics & Cancer

Advances in molecular diagnostics are at the heart of the area of health care often referred to as personalized, or precision, medicine. In precision medicine, our increasing understanding of the underlying molecular mechanisms of disease is used to stratify patients into increasingly narrow sub-populations based on specific disease characteristics that can be addressed with correspondingly specific treatments.

Advances in diagnostics technologies and in our fundamental understanding of the mechanisms of cancer at a molecular level are driving the development of new treatments and diagnostic tests. While molecular diagnostics are still a small part of the whole field of diagnostics — already a cornerstone of health care — they already are a critical and transformative component of cancer care.

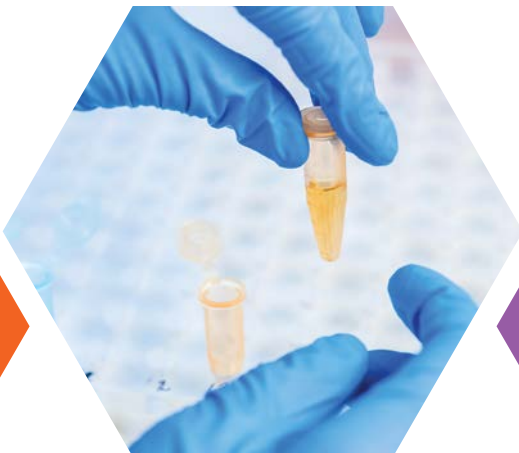
Molecular diagnostics can assess a person’s risk of developing a disease, determine whether a person is a carrier of a hereditary condition, screen for diseases that are present but not yet symptomatic, provide a diagnosis of existing symptoms, or monitor how a patient is responding to treatments.

Companion diagnostics is the relatively new term describing the tests — often molecular — that are used to determine whether a specific therapy would likely be effective for a specific patient. These tests improve patient outcomes, and can reduce health care costs, by helping to ensure that patients get the right treatment the first time and reducing the number of patients who use a therapy that is ineffective for them.⁴

The specific and actionable insights that molecular diagnostics provide at every stage of care make them one of the most dynamic and transformative areas of diagnostics and in health care.

In order to better appreciate the specific applications of molecular diagnostics to detect cancer and inform treatment decisions, it is helpful to first understand the basics of human genetics and cancer biology.

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Genetics

DNA (deoxyribonucleic acid) is the inherited material found in almost every living cell that governs the way our bodies develop and function. DNA is composed of two interlocking, helical strands, each of which is made up of a string of four molecules in varying sequence: adenine (A), guanine (G), cytosine (C), and thymine (T). Adenine on one strand pairs with thymine on the opposite strand, and guanine pairs with cytosine forming what are referred to as “base pairs.”

Each complete human DNA helix contains a sequence of about three billion base pairs. The sequence of the bases is more than 99% identical in all people. The remaining one percent variability is responsible for the differences that occur among individuals. Our genes, which are the functional units of heredity, are segments of the DNA strand that range in size from a few hundred bases to more than 2 million bases.⁵

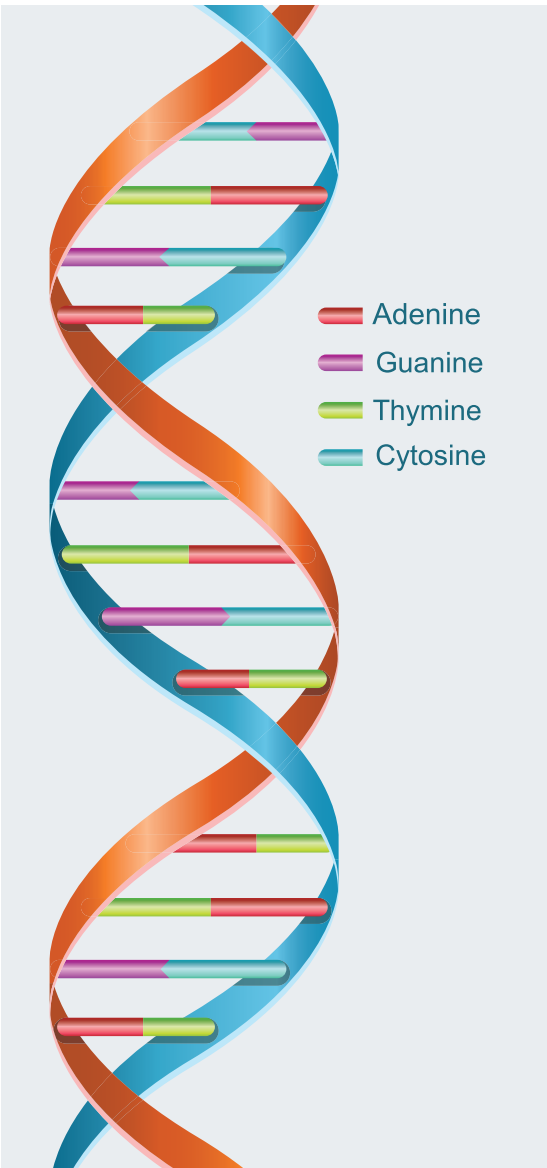
DNA is copied into RNA (ribonucleic acid) through a process called transcription. The sequence of this RNA is then edited to remove unnecessary information and translated into a sequence of amino acids — the building blocks of proteins that make up part of the machinery of our cells — and, consequently, the structures and functions of our bodies. This protein production is referred to as the expression of genes. RNA that is not expressed into proteins remains to play a regulatory function in the cell. The complex specialization, or differentiation, of cells throughout the body is a result of specific genes being active in certain cells at certain times, and therefore expressing proteins related only to the functions of those cells. Differences in genes among individuals, and the variable expression of those genes in a given individual, account for the physiological diversity of our race, as well as many of our diseases and health conditions.

An essential cellular function is DNA replication, in which the helix separates and each strand is duplicated. This is how an exact copy of an individual’s DNA is transferred from one cell to another during cell division.

Genetic errors, or mutations, can occur at any time during a cell’s life. While some mutations are harmless, others can affect the expression of the particular gene in which it exists, which can result in dysfunction and disease — such as cancer. A mutation can be an added, deleted, substituted, or rearranged base pair that prevents cellular processes driven by that gene from functioning properly, from happening at all, or from occurring too irregularly and frequently. There are inherent cellular mechanisms to repair genetic errors, but they are not perfect and can even cause further damage to the genetic code.⁶

There are three kinds of gene mutations, which may be a change of only one base or a long sequence of bases. These are (1) hereditary — a mutation that is passed from parent to child; (2) de novo — new mutations that arise in the egg or sperm cell, or shortly after fertilization, and so are repeated throughout the body; or (3) somatic — those that arise in regular body cells due to environmental causes or through an error in DNA replication. Somatic mutations are the mutations most often found in cancerous cells, though there are several important cancer-related gene mutations that are known to be hereditary. A good example is mutations to the BRCA1 and BRCA2 genes, which increase the risk of female breast and ovarian cancers and can be inherited from either a mother or father who carries that mutation.¹⁰





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GENE NAMES

The names of genes used when talking about molecular diagnostics can be confusing. Genes are given names that describe what they do in the body, which can be full of scientific jargon. Most often, you will see genes referred to by their abbreviations (“symbols”) and a set a letters and numbers that describe the mutation.⁷ For example, a patient with melanoma may be told they have a V600E mutation in their BRAF gene. BRAF is the gene symbol for the B-raf proto-oncogene serine/threonine kinase gene. The long name explains what a gene does — which in this case, is to produce the B-raf protein, which plays a role in transmitting chemical signals from the outside to the inside of a cell.⁸ “V600E” provides details of the mutation. This mutation occurs at position 600 in BRAF where a base pair substitution results in the amino acid valine (“V”) being replaced by a glutamic acid (“E”), which then alters the function of the gene and can potentially make it cancerous.⁹

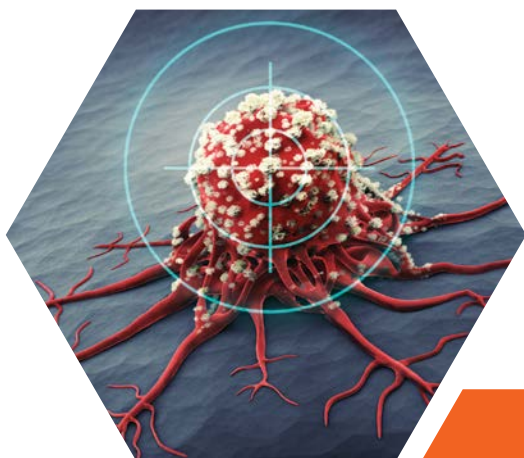


Cancer Biology

Rather than a single disease, cancer is a collection of diseases characterized by uncontrolled cell growth which is caused by the dysregulation of processes that control normal cell multiplication and death.² This is the result of mutations or epigenetic changes (see the following section) in the genes that control the way cells function. Therefore, specific cancers can be characterized by unique underlying molecular mechanisms and so we increasingly understand and identify cancers by those mechanisms rather than by their original location in the body.

Humans grow from a single cell at conception to an estimated 37.2 trillion cells in adulthood by going through extensive cell multiplication.¹¹ The pace of multiplication slows as a person matures, until eventually normal cells multiply only to replace cells that have died as a result of normal wear and tear or external factors.

The uncontrolled growth of cells that cause cancerous tumors is initiated by mutations in DNA.



The breakdown of normal cell processes that occurs in cancerous cells allows cells to multiply uncontrollably, avoid apoptosis (i.e. genetically 'programmed' cell death), and accumulate to form solid tumor masses. Once a malignant, or cancerous, tumor forms, its environment affects what happens next. Some cellular and tissue environments permit tumors to develop the ability to metastasize, or spread, to other places in the body by breaking off and traveling through the blood or lymph systems.

The uncontrolled growth of cells that cause cancerous tumors is initiated by mutations in DNA. There are several gene types that are common "drivers" of cancer:

- ▲ Proto-oncogenes are genes that normally promote cell growth and division. When mutated, these genes — now called oncogenes — are turned 'on' even when they shouldn't be, which allows the cell to grow uncontrollably.¹² When this happens, tumors can form.
- ▲ Tumor suppressor genes are the genes that normally prevent cells from dividing too quickly, repair DNA mistakes, and tell cells when to die.¹² These genes become cancerous when altered in a way that inactivates them, so that cells grow out of control.

As mentioned before, not all mutations cause cancer — but as the human body ages, and accumulates more and more mutations over time, the chance of some of those mutations causing cancer increases.

BIOMARKERS

A biomarker is a biological molecule that, when measured in the body, can indicate the presence of normal or pathogenic processes.¹³ Molecular diagnostic tests identify an existing cancer, or the likelihood of an individual developing a certain type of cancer, by analyzing specific biomarkers. Tests may search only for certain gene variants, or map the entire sequence of a targeted portion of DNA to detect all mutations in the sequence.⁵

Cancer biomarkers typically are changes in genetic structures or proteins (or levels of proteins) that are associated with cancer and can be objectively measured. As applied in cancer care, molecular diagnostics identify and measure those cancer biomarkers in order to predict the likelihood that an individual will develop a certain type of cancer, identify an existing cancer, measure how far the cancer has progressed and inform a prognosis, indicate which treatment option may work best, determine the risk that the cancer may reoccur, and/or monitor the progress of the disease or treatment.

Epigenetics and Cancer Development

The development of cancer can also occur as a result of epigenetic changes. Epigenetic changes are different from mutations, because they affect gene expression without altering the genetic base sequence.¹⁴ Like mutations, epigenetic alterations can be inherited or acquired.

Common epigenetic changes include chemical alteration of the DNA structure, modification of histones — the proteins that package DNA in the cell nucleus — and interference by small RNA pieces that affect gene expression. While epigenetic modifications are a normal part of the human genome, abnormal and unprogrammed changes can disrupt the normal functioning of the cell and lead to disease.

Cancer was one of the first diseases to be linked to epigenetics in the early 1980s.¹⁴ Since then, epigenetic changes have been shown to play a role in every stage of carcinogenesis, including tumor initiation.¹⁵ Epigenetics may be the factor

that explains why some individuals do not develop cancer, even if they have the same genetics as those who did develop the disease.

One of the most common epigenetic mechanisms found in cancerous cells is inappropriate DNA methylation. DNA methylation — which is the addition of a methyl (-CH₃) group to a DNA base — plays an important role in the expression of genes and controlling which genes are turned ‘on’ and ‘off.’ In cancer, hypomethylation can activate oncogenes, while hypermethylation can silence tumor suppressor genes, allowing tumors to form.¹⁴

These abnormal methylation patterns have been found to be both cancer type-specific and tumor-stage specific. Some modifications can even be detected before a tumor starts to develop.¹⁵ Therefore, epigenetic changes, such as methylation, can be considered biomarkers for diagnostic, prognostic, and therapy selection testing. In addition, many epigenetic changes are reversible. This has made epigenetic mechanisms important targets for new diagnostic tests and therapies.

MOLECULAR DIAGNOSTICS TECHNOLOGY AND GENETIC TESTING

A number of techniques are employed in modern diagnostics to detect and quantify specific DNA or RNA sequences, as well as proteins. The most fundamental technique is polymerase chain reaction (PCR), which is a method used to amplify DNA or RNA sequences until there are so many copies that they can be detected and measured. Tests may search only for certain gene variants or map the entire sequence of a targeted portion of DNA — including the whole genome if desired — to detect all mutations in the sequence.⁵

PCR is a powerful tool for locating short segments of a gene where known critical mutations or variances can lead to altered cell functions associated with disease or altered function. PCR tests for the presence of a portion of DNA that has a known base sequence, a DNA “marker” associated with the gene of interest, employing the same enzymatic process used by natural DNA replication to rapidly amplify, or copy, that sequence until there are thousands or millions of copies. Because PCR relies on amplification, it is highly sensitive, meaning it can detect specific DNA segments that may be present at very low levels in the sample.⁵

Once the DNA is amplified, it can be analyzed in multiple ways depending on the desired result. The DNA can be measured just for size to check for large deletions or insertions of DNA, measured for abundance, or assessed base by base to determine the sequence of the DNA sample in order to locate potential biomarkers.



Cancer Diagnostics in Practice

Molecular diagnostics are an important decision-making tool in every stage of cancer treatment and care, from screening patients who may be at a high risk for cancer to assessing the risk of a person developing a certain cancer to monitoring a patient during and following treatment. Instead of treating every person with cancer the same way, clinicians now have the tools to personalize testing and treatment along the entire care pathway.

Risk assessment: Diagnostic tests can be used to search for biomarkers that indicate an elevated risk of developing the corresponding cancer. For example, women with certain variations in the BRCA1 or BRCA2 genes have up to an 85 percent lifetime chance of developing breast cancer, compared with a 13 percent lifetime chance among women who do not have those gene variations.⁴ Women can be screened with a molecular diagnostic for BRCA1/BRCA2 to see if they carry mutations in those genes. This screening is especially important for women with traditional breast cancer risk factors, such as a family history of the disease. If a woman tests positive for a mutation, she has several options on how to proceed, such as scheduling more frequent mammograms.

Screening: Screening tests may be conducted for patients at high risk of a certain cancer, or for cancers for which routine screening is advised, in order to identify the disease as early as possible. A common example is testing for the human papilloma virus (HPV), which has been strongly linked to cervical cancer. In the past, most cases of cervical cancer were discovered through routine Papanicolaou (Pap) smears.⁵ Now there are molecular diagnostic tests that can identify the subtypes of HPV that carry the greatest risk of developing into cervical cancer. A woman can find out, before receiving an abnormal or inconclusive Pap smear result, that she has high-risk HPV that may later cause the cellular abnormalities that mark the beginning of cervical cancer development. This information allows her and her doctor to take precautions, such as scheduling more frequent pelvic exams and following up more aggressively to an inconclusive or abnormal Pap smear, to catch the development of cervical cancer as early as possible — if it develops.

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Diagnosis: Tests for diagnosis are used to obtain a definitive diagnosis and for general cancer typing. Tests may measure the presence, levels, or activities of specific proteins or genes in tissue, blood, or other bodily fluids in order to detect cancer, or classify it into a subtype. For example, in acute myeloid leukemia, a cancer of the bone marrow, certain diagnostic tests can be used to examine the specific gene mutations in a leukemia cell. There are multiple subtypes of leukemia, with different and unique combinations of biomarkers.¹⁶ Identifying the correct subtype, by examining the gene mutations, will guide treatment options for a particular patient.

Staging and Prognosis: Staging or prognostic tests are used to assess the severity of the cancer and/or the risk of recurrence. They can help inform a decision, for example, regarding how aggressive initial treatment should be given a particular risk of recurrence, in hopes of preventing that recurrence. For example, there are multimer diagnostic tests that can inform colon cancer patients of the risk of their cancer returning after surgery by examining the unique biology of a patient's colon tissue and its genetic profile.⁵ These tests place patients into risk categories that help guide therapy decisions, and can inform physicians whether or not more aggressive treatment is needed.

Therapy Selection: There are an increasing number of molecular diagnostic tests that can indicate which treatments and therapies may work most effectively, or rule out those that are unlikely to work, for a certain patient. For example, K-Ras testing is done to detect KRAS mutations, which are found in pancreatic, colorectal, lung, and other cancers. Approximately 40 percent of colorectal cancer patients with a KRAS mutation will not respond to the anti-EGFR class of drugs most often used for colorectal cancer.¹⁷ Current practice guidelines now recommend these drugs only for patients with normal, non-mutated KRAS genes.¹⁸ Another example of a diagnostic test to guide therapy selection is the BRAF gene in melanoma. The drug vemurafenib only works in patients who test positive for the V600E BRAF mutation, so testing for that specific mutation before choosing vemurafenib is a necessity.¹⁹

Monitoring: Monitoring tests can tell a patient and their doctor whether or not a treatment is working, or give them information about the likelihood of recurrence. For patients with chronic myelogenous leukemia, a type of blood cancer, physicians may use do a mutation analysis that looks for new mutations in the BCR-ABL gene during the course of treatment.²⁰ This test may be done multiple times as treatment progresses in order to monitor its effectiveness and inform a decision whether or not to modify treatment accordingly.



Managing Health Care Costs

Not only can appropriate use of diagnostic tests significantly improve health care outcomes, but improving care through diagnostic testing also can ensure more effective allocation of health care spending. In 2010, the United States spent an estimated \$125 billion on the direct medical costs of cancer care and cancer costs may be as high as \$156 billion per year by 2020.²¹ Diagnostic testing and the use of personalized medicine can reduce costs by catching cancer in its early stages and enabling earlier interventions that can be more effective, reducing unnecessary or ineffective treatments, and guiding treatment that is more likely to prevent reoccurrences. For example, testing for the KRAS gene prior to the treatment of metastatic colorectal cancer can avoid hundreds of millions of dollars per year of spending on treatments that have been shown to be ineffective in patients with a mutated KRAS gene.^{22,23,24}



The Future of Diagnostics and Cancer Care

Molecular diagnostics have transformed the way we approach cancer care, and promise to be a critical contributor to further progress. Because of better diagnostic tests, patients are receiving more effective care and living fuller, longer lives during and after their cancer diagnoses.

However, the sheer number of people being diagnosed with cancer each year in the U.S. continues to rise, and cancer remains a significant public health challenge in part because advances in cancer care have not been uniform across all types of cancer, or among all patients with a certain cancer.² Survival rates are affected by the type of cancer, stage at diagnosis, and patient demographics. There is a need for the continued discovery of new biomarkers to fully characterize the many subsets of cancer patients.

Next generation sequencing (NGS) — new gene sequencing technologies that improve speed and accuracy — is becoming more widespread, reducing the amount of time and money it takes to either identify specific gene sequences or to sequence a patient’s entire genome.²⁵ The ability to more efficiently generate genetic data is advancing our knowledge of cancer genomics by more rapidly uncovering previously unknown genetic variants associated with cancer.¹³

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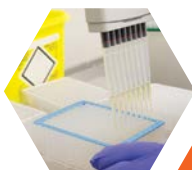


Large scale research programs, including those using NGS, already have identified a significant number of mutations or other molecular alterations in different cancers that could be potential biomarkers for new diagnostics and targets for new therapies and drugs.¹³ Further research is needed to identify the significance and potential of each of these biomarkers. In early 2015, the Obama Administration recognized the need to increase investment in this area and announced the Precision Medicine Initiative. The Precision Medicine Initiative seeks to advance research and technology in order to enable researchers, providers, and patients to work together to develop individualized care. This initiative includes significant funding for the National Cancer Institute to advance the field of precision oncology.²⁶

In addition to the challenges of continued research and innovation, molecular diagnostics face significant regulatory and insurance coverage and reimbursement hurdles that can slow test development and timely patient access.

There are growing expectations among payers and health systems for test developers to provide greater evidence of a test's clinical utility (a measurement of the effect that a test result has on medical decision making, possibly including clinical outcomes), in addition to its analytical validity (conformance to claimed accuracy or precision) and clinical validity (how relevant the tested biomarker is to the disease state in question). However, generating this evidence for diagnostic tests has unique challenges compared to a similar assessment for a treatment. Tests provide information, so their impact on the patient is indirect and may not be easily quantified. The impact of a test result on a patient also is dependent on what the physician and patient decide to do with that information, and the benefit of a test result also can be undermined by various shortcomings within the health care system. A recent report from the Institute of Medicine, "Improving Diagnosis in Health Care," highlighted these systemic challenges.²⁷

Despite the challenges noted here, molecular diagnostics are driving tremendous advances in cancer care. The field of molecular diagnostics will continue to leverage the cutting edges of science and technology to provide powerful information guiding the diagnosis and treatment of individual cancer patients.



About AdvaMedDx

The world’s leading diagnostics manufacturers established AdvaMedDx to advocate for the power of medical diagnostic tests to promote wellness, improve patient outcomes, and advance public health in the United States and abroad.

AdvaMedDx member companies represent one of the most dynamic and innovative sectors in the health care system. Diagnostics are at the forefront of medical innovation and influence every aspect of health care decision-making, providing critical insights at every stage of care — prevention, detection, diagnosis, treatment, and successful health management.

The appropriate use of diagnostic tests:

- ▲ Promotes wellness
- ▲ Enables earlier, personalized, and more effective health interventions
- ▲ Improves patient care and outcomes
- ▲ Advances public health
- ▲ Ensures effective allocation of health care spending

AdvaMedDx member companies produce innovative, safe, and effective tests that are performed in laboratories, at the hospital bedside, in doctor’s offices, in medical clinics, in triage settings, and even in the home — in every setting in which accurate information about an individual’s health status is needed.

For more information, please visit AdvaMedDx.org.



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