

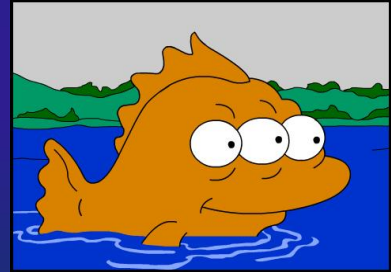
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Current Status of the Use of Molecular Genetics and Tumor Markers in Cancer Diagnosis, Workup and Treatment

2019-2020 FCDS ANNUAL WEBCAST SERIES

FEBRUARY 20, 2020

STEVEN PEACE, CTR



CDC & Florida DOH Attribution

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FLccSC LMS – CEU Quiz –FCDS IDEA



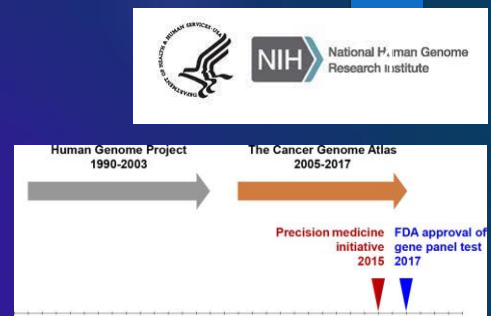
- ▶ Attendees must take and pass a 3-5 question CEU Quiz to get CEUs
- ▶ CEU Awards are Restricted to Attendees with a FLccSC LMS Account
- ▶ The CEU Quiz will be posted to FLccSC 1-2 hours after the webcast ends

- ▶ Only registered FLccSC Users will be given access to the CEU Quiz
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- ▶ Attendees can attend any of the live webcasts without receiving CEUs
- ▶ Recorded Sessions are also available for non-FLccSC Users – No CEUs

Presentation Outline

- ▶ Background of Genetic Testing
- ▶ Clinical Applications for Genetics Testing
- ▶ Who Pays for The Test(s) and Circumstances
- ▶ Single Gene Testing – First Steps
- ▶ Proliferation of Multi-Gene Testing
- ▶ Genetic Counselling – Yes or No??
- ▶ Direct to Consumer Marketing – Is it Worth the Price of Testing?
- ▶ Does Next Generation Sequencing Effect Testing?
- ▶ Can a Different Gene Test Result Change the Histology Code?
- ▶ Explosion of Genetic Testing Companies/Products
- ▶ Proliferation of Proprietary Multi-Gene Testing Panels
- ▶ Does the FDA Regulate Gene Tests and Genetic Panels
- ▶ How To Standardize a Panel When There Are Thousands of Genes?
- ▶ Questions



Background



NIH National Human Genome Research Institute

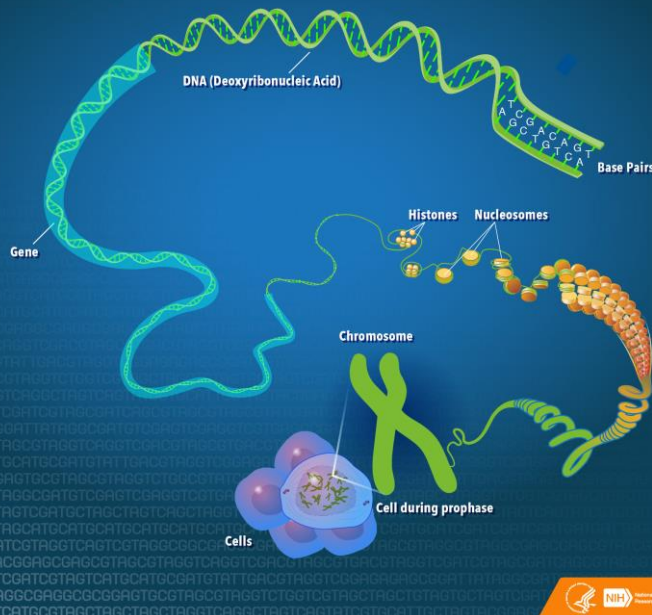
- ▶ Knowledge of cancer genetics is rapidly improving our understanding of cancer biology, helping identify at-risk individuals, furthering our ability to characterize malignancies, establishing treatment tailored to the molecular fingerprint of the disease, and leading to the development of new therapeutic modalities.
- ▶ Prevention, screening, classification, and treatment is just the starting point for research.
- ▶ The Human Genome Project was an international scientific research project with the goal of determining the base pairs that make up human DNA, and of identifying and mapping all of the genes of the human genome from both a physical and a functional standpoint.
- ▶ Beginning on October 1, 1990 and completed in April 2003, the HGP gave us the ability, for the first time, to read nature's complete genetic blueprint for building a human being.
- ▶ Science and technology have expanded beyond comprehension in general medicine, diagnostics and treatment in many health specialties including; cancer, diabetes and heart disease and allowed 'personalized medicine' to become a new reality in some diseases.
- ▶ Pharmacogenetics is rapidly expanding secondary to genetic discoveries.
- ▶ Plus research and discovery into single and polygenetic diseases continues.



A BRIEF GUIDE TO GENOMICS

NHGRI FACT SHEETS
genome.gov

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Clinical Applications for Genetic Testing

- ▶ Evaluating individual risk of disease – individual genetics
- ▶ Evaluating family risk of disease – family genetics
- ▶ Enhancing the classification of health conditions including cancers
- ▶ Development of highly specialized treatments for specific health conditions
- ▶ Monitoring or early detection of numerous health conditions before/after symptoms
- ▶ Monitoring or early detection of specific health conditions in special populations
- ▶ Monitoring or early detection of cancer;
 - ▶ Understanding the genetic basis of a cancerous tumor to help guide the most effective treatment;
 - ▶ Track the effectiveness of cancer treatment, informing treatment to be adjusted to optimize effect.
- ▶ Each human has about 21,000 genes in their individual genome with dozens of potential building block 'letters' (A, T, C, and G) that make you and me unique.

Clinical Applications for Genetic Testing

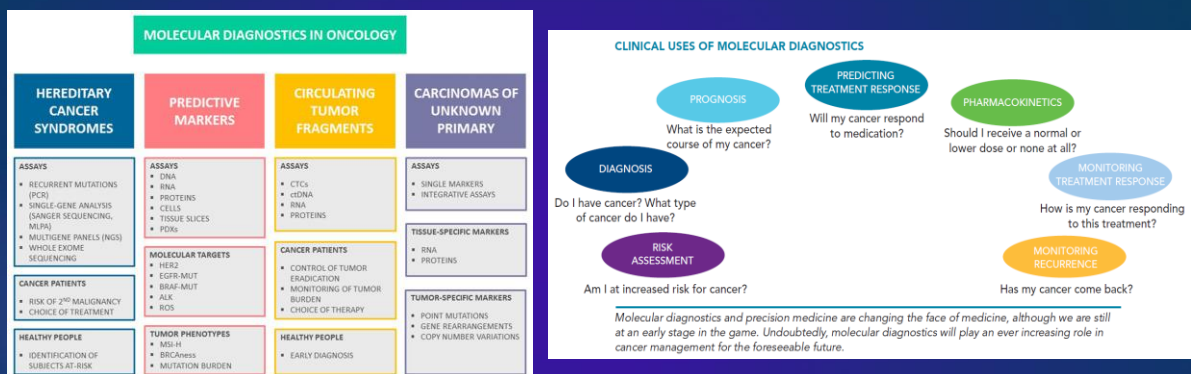


FIGURE 1 | Molecular diagnostics in oncology. There are several major avenues in cancer medicine, which utilize molecular-based assays. Testing for hereditary cancer syndromes is now routinely used both for identification of persons at-risk and for personalization of systemic treatment. There is a number of predictive tests involving either the analysis of individual drug targets or identification of specific tumor phenotypes, which aid the choice of anticancer drugs. Monitoring of malignant disease can be achieved through molecularly-driven detection of residual tumor fragments; it is anticipated that liquid biopsy will serve as an instrument for early cancer diagnosis and screening in the future. Recent developments in the mutation testing and RNA analysis offer novel tools for diagnosis of cancers of unknown primary site. (SOURCE: Frontiers in Molecular Biosciences | www.frontiersin.org/Molecular Tests in Oncology – August 2018/Vol 5, Article 78)

Can a Different Gene Test Result Change the Histology Code?

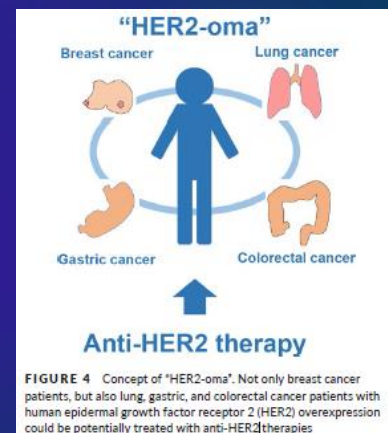
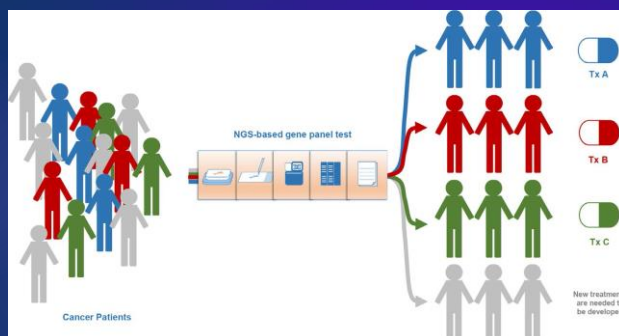
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- ▶ YES AND NO – IT DEPENDS AND IT WILL CONTINUE TO CHANGE AS WE LEARN.
- ▶ STILL – MOST of the ICD-O Histology Codes do not have genetic data in them
- ▶ HOWEVER – Increasingly, myeloid neoplasms have genetic data in codes
- ▶ HOWEVER – Increasingly, brain tumors have genetic data in codes
- ▶ If you get down to the nitty gritty – there will be something unique about every single tumor – so, heed the following WARNING...
- ▶ WARNING – Soon we will have multiple genetic abnormalities and it will be more difficult to distinguish one from another based on genetics and we will have to decide which genetic mutations are important and which are not.

Diffuse intrinsic pontine glioma, H3 K27M-mutant
 Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation
 Ependymoma, RELA fusion-positive
 Astrocytoma, anaplastic, IDH-mutant
 Astrocytoma, anaplastic, IDH-wildtype
 Oligodendroglioma, anaplastic, IDH-mutant and 1p/19q codeleted
 Medulloblastoma, SHH-activated and TP53-wildtype
 High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
 Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1
 Mixed phenotype acute leukemia with t(v;11q23); MLL rearranged
 B lymphoblastic leukemia/lymphoma with iAMP21
 B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1
 B lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged
 B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)
 B lymphoblastic leukemia/lymphoma with hyperdiploidy
 B lymphoblastic leukemia/lymphoma with hypodiploidy(Hypodiploid ALL)
 B lymphoblastic leukemia/lymphoma with t(5;4)(q31;q32); IL3-IGH
 B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)
 B lymphoblastic leukemia/lymphoma, BCR-ABL1-like
 Acute myeloid leukemia, CBF-beta/MYH11
 Acute myeloid leukemia, inv(16)(p13;q22)
 Acute myeloid leukemia, t(16;16)(p13;q11)

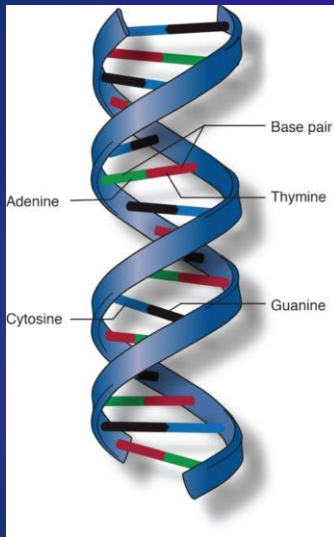
Can a Different Gene Test Result Change the Histology Code?

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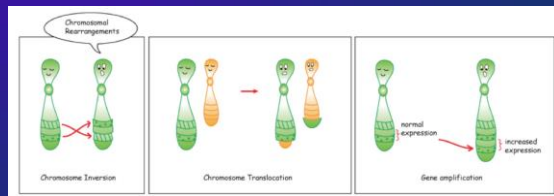
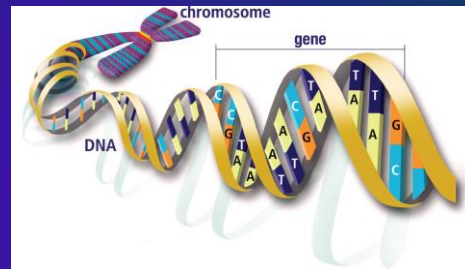


Chromosome, DNA, and Genes

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CHROMOSOME, DNA, AND GENE



Who Pays for The Test(s) and Under What Circumstances

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- ▶ The cost of genetic testing can range from under \$100 to more than \$2,000, depending on the nature and complexity of the test. The cost increases if more than one test is necessary or if multiple family members must be tested to obtain a meaningful result. Genetic Discrimination.
- ▶ Health insurance providers have different policies about which tests are covered. A person interested in submitting the costs of testing may wish to contact his or her insurance company beforehand to ask about coverage. It may cost you a lot more than you first think it will.
- ▶ Some people may choose not to use their insurance to pay for testing because **the results of a genetic test can affect a person's insurance coverage**. Instead, they may opt to pay out-of-pocket for the test. People considering genetic testing may want to find out more about their state's privacy protection laws before they ask their insurance company to cover the costs.
- ▶ Health insurance typically pays for genetic counseling and in many cases pays for genetic testing when it is recommended by a doctor. However, it is important to check with your insurance company to verify coverage. Insurance companies have different policies, and may cover some tests, but not others.
- ▶ Currently genetic tests cost taxpayers well in excess of \$500M a year with little benefit.

Single Gene Testing – First Steps

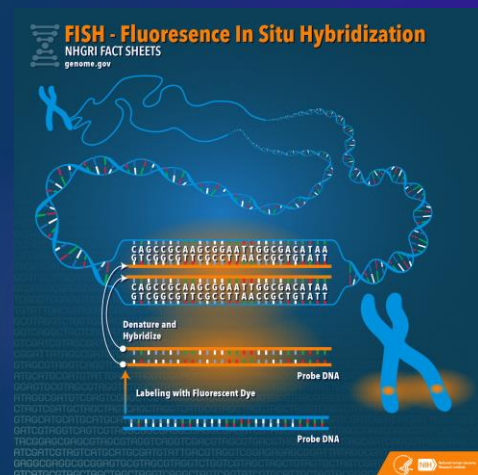
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- ▶ Single gene testing is done when your doctor believes you or your child have symptoms of a specific condition or syndrome.
- ▶ Single gene testing is also used when there is a known genetic mutation in a family – post-natal or hereditary cancer diagnoses.
- ▶ Indications for single gene testing
 - ▶ High clinical suspicion for a specific gene to be causative for a patient's clinical presentation
 - ▶ Previous negative genetic testing did not include analysis of a specific gene of interest
 - ▶ Single gene testing may be cost-effective and minimize the need for testing unnecessary genes that are not of interest.
 - ▶ Single gene testing may reduce the chance of learning about health risks that are unrelated to the current clinical concern.

GENE	POSTNATAL GENE PANELS										HEREDITARY CANCER PANELS									
	A	CTD	C	CL	DMD	EDS	GH	HA	HA	HA	HA	B	B	NOU	C	EPF	N	P	R	C
BBST10																				
BBST12																				
BDNF																				
BDNF																				
BLM																				
BMP1																				
BMPRTA																				
BRAF																				
BRCA1																				
BRCA2																				
BRP1																				
C1R																				
C1S																				
CACNA1C																				
CASK																				
CASR																				
CCN1																				

Fluorescence (FISH) vs Microarray

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Fluorescence in situ hybridization (FISH) provides researchers with a way to visualize and map the genetic material in an individual's cells, including specific genes or portions of genes. This may be used for understanding a variety of chromosomal abnormalities and other genetic mutations.

For many applications, **FISH has largely been replaced by the use of microarrays**. However, FISH remains useful for some tests.

FISH is useful, for example, to help a researcher or clinician identify where a particular gene falls within an individual's chromosomes. The first step is to prepare short sequences of single-stranded DNA that match a portion of the gene the researcher is looking for. These are called probes. The next step is to label these probes by attaching one of a number of colors of fluorescent dye.

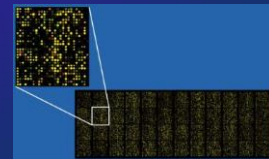
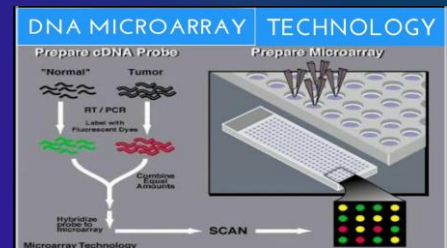
DNA is composed of two strands of complementary molecules that bind to each other like chemical magnets. Since the researchers' probes are single-stranded, they are able to bind to the complementary strand of DNA, wherever it may reside on a person's chromosomes.

When a probe binds to a chromosome, its fluorescent tag provides a way for researchers to see its location.

Microarray is a DNA lab-on-a-chip

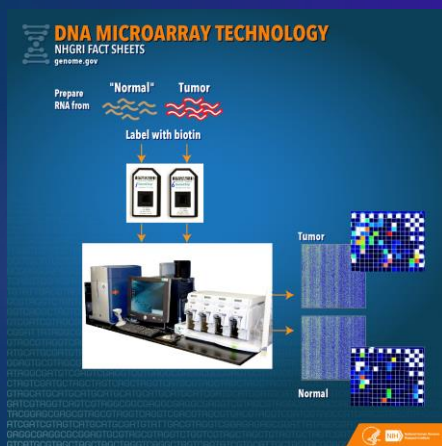
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- ▶ A DNA microarray is a collection of microscopic DNA spots attached to a solid surface.
- ▶ It is a multiplex lab-on-a-chip. It is a two-dimensional array on a solid substrate that assays large amounts of biological material using high-throughput screening miniaturized, multiplexed and parallel processing and detection methods
- ▶ Scientists use DNA microarrays to measure the expression levels of large numbers of genes simultaneously or to genotype multiple regions of a genome.
- ▶ DNA microarrays have become the most sophisticated and the most widely used type of 'chip microarray', while the use of protein, peptide and carbohydrate microarrays is expanding.



Large Scale DNA Microarrays Using New DNA Sequencing Tools

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When they were first introduced, DNA microarrays were used only as a research tool. Scientists continue today to conduct large-scale population studies - for example, to determine how often individuals with a particular mutation actually develop breast cancer, or to identify the changes in gene sequences that are most often associated with particular diseases. This has become possible because, just as is the case for computer chips, very large numbers of 'features' can be put on microarray chips, representing a very large portion of the human genome.

Microarrays can also be used to study the extent to which certain genes are turned on or off in cells and tissues. In this case, instead of isolating DNA from the samples, RNA (which is a transcript of the DNA) is isolated and measured.

Today, DNA microarrays are used in clinical diagnostic tests for some diseases. Sometimes they are also used to determine which drugs might be best prescribed for particular individuals, because genes determine how our bodies handle the chemistry related to those drugs.

With the advent of new DNA sequencing technologies, some of the tests for which microarrays were used in the past now use DNA sequencing instead. But microarray tests still tend to be less expensive than sequencing, so they may be used for very large studies, as well as for some clinical tests.

Next Generation Sequencing (NGS) 17

- ▶ We have spent a lot of time discussing the emerging multi-gene profiles that are coming out where most pathologists agree to a small cell of multiple genes to be tested – because they are already directly linked to an available specific gene-based treatment.
- ▶ BUT – We are also seeing dozens and dozens of super-multi-gene testing profiles being tested with anywhere from 2 dozen to 750,000 base pairs being tested all at once – and then what to do with results.
- ▶ Cancer panels use **next generation sequencing (NGS) technology** to target specific genes or mutations that have established relevancy to a particular cancer phenotype. ... LOTS OF NEW GENETIC RESEARCH COMPANIES offers a DOZENS and DOZENS of different cancer panels to provide a complete solution from experimental design to advanced bioinformatics analysis.
- ▶ This high-throughput DNA sequencing technology can sequence an entire human genome within a few hours at a cost of just around \$1000.00. US.
- ▶ NGS technology can be powerful enough to discover new and infrequent gene alterations, identify hereditary cancer mutation carriers and provide a reliable molecular portrait of wide range of cancers in a quick and cost-effective manner.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6277731/>

Proliferation of Multi-Gene Testing 18

- ▶ Multigene panel testing is a type of genetic testing that looks for mutations in several genes at once.
- ▶ This is different from single-gene testing, which looks for a mutation in a specific gene.
- ▶ Note: Single-gene testing is used when there is already a known gene mutation in a family. For example, testing for BRCA mutations only looks for changes in BRCA1 and BRCA2 genes.
- ▶ Multigene panel testing may be useful if you
 - ▶ are at risk of a family cancer syndrome that has more than one gene associated with it
 - ▶ have a personal or family history of cancer and single-gene testing has not found a mutation, or the result is uncertain
- ▶ The risks of multigene panel testing may include the following:
 - ▶ Results can be complicated to interpret.
 - ▶ Testing may find gene mutations that show a moderate or uncertain risk of cancer.
 - ▶ It may be hard to know what you should do with your test results.
 - ▶ You should talk with a genetic counselor or physician expert before and after genetic testing to learn what the results mean.

What is Next for the Next-Next Generation of Sequencing

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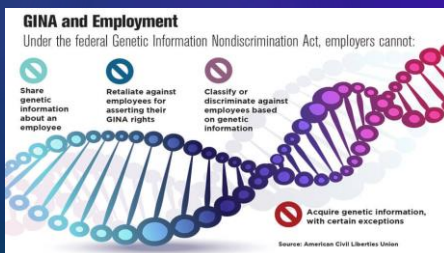
- ▶ Southern blot
- ▶ Dot blot/Reverse dot blot
- ▶ Polymerase chain reaction
- ▶ SSCP/DGGE
- ▶ RT-PCR
- ▶ DNA sequencing
- ▶ TaqMan, real-time PCR
- ▶ Invader assay
- ▶ In situ hybridization
- ▶ Microarray hybridization
- ▶ High-density microarray hybridization
- ▶ Array comparative genomic hybridization
- ▶ Whole-genome sequencing



Employment and Health Insurance

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- ▶ **WARNING:** Many people are concerned about possible employment discrimination or denial of insurance coverage based on genetic testing results.
- ▶ **The Genetic Information Nondiscrimination Act of 2008 (GINA ACT) makes it illegal for health insurers to require genetic testing results or use results to make decisions about coverage, rates, or preexisting conditions.**
- ▶ **GINA also makes it illegal for employers to discriminate** against employees or applicants because of genetic information.
- ▶ **GINA does not apply to** life insurance, long-term care insurance, or disability insurance.



ACLU – Judge Sweet issues Ruling, March 29, 2010. Myriad appeals the decision to Court of Appeals for the Federal Circuit. Depending on that outcome, case could be appealed to the U.S. Supreme Court.

"DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature."

"DNA's existence in an isolated form alters neither this fundamental quality...nor the information it encodes."

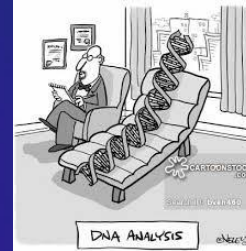
"Therefore, the patents at issue directed to 'isolated DNA' containing sequences found in nature are unsustainable as a matter of law and are deemed unpatentable subject matter under 35 U.S.C. §101."

Genetic Counseling – Yes or No

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Genetic Counseling is a process of individualized or personalized communications between genetics professionals and patients with the goal of providing individuals and families with information on the relevant aspects of their genetic health, available genetic testing, and management options to support them in their daily lives.

- Family and Medical History – implications for whole family
- Analysis of Genetic Information
- Communication of Genetic Information
- Education about inheritance, gene testing, management of results, risk reduction, available and alternate resources and state of the research
- Supportive counselling to facilitate informed choices, decisions, and acknowledgement and adaptation to any risk or condition(s) identified
- Follow-Up
- May involve genetic counselor, advanced practice genetics nurse, medical geneticist, mental health professional and other medical experts such as oncologist, surgeon, or internist

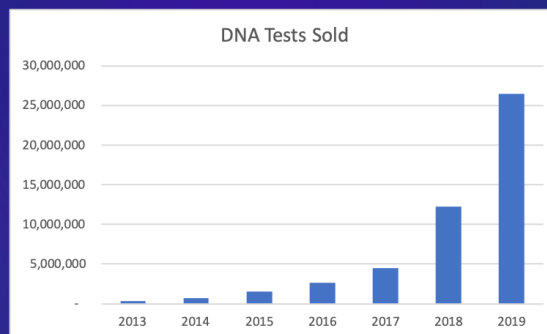


- Have you or any family members been diagnosed with cancer?
- If yes, which family members were diagnosed, with what types of cancer, and at what ages?
- Who in your family could potentially get tested
- Were you or any of your family members born with birth defects?
- Are you of Eastern or Central European Jewish ancestry?
- How testing is done
- What the test results may mean
- What you may do depending on the results

Direct to Consumer Marketing - Is it Worth the Price of Testing?

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Our test with match your DNA with 642,824 genetic markers – and?



Direct to Consumer Marketing - Is it Worth the Price of Testing?

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- ▶ Ancestry
- ▶ Community
- ▶ Family History
- ▶ Personal Identity & Traits
- ▶ Health & Wellness Information
- ▶ Nutrition, Weight and Metabolism
- ▶ The Health DNA Market – CAUTION !!
- ▶ You might want Genetic Counsellor to Help.



Rank services by these 10 factors:

- 1) Company Reputation
- 2) Services Offered
- 3) Testing Method
- 4) Software Grade
- 5) Research & Scientific Evidence
- 6) CLIA Compliance
- 7) Customer Reviews
- 8) Price
- 9) Customer Service
- 10) Return Policy

- ▶ Advances in gene sequencing technologies also identify variants in genetic sequence testing, along with findings not related to the disorder being tested. These are incidental or secondary findings. These findings are a major source of clinical, ethical, legal and counseling debate as well as making decisions as to when and what results should be provided to patients and to their healthcare providers and with what level of certainty.
- ▶ ASK and CHECK ON SECURITY PROCEDURES FOR YOUR DNA INFORMATION!!
- ▶ HOW IS YOUR DNA USED – IS IT PRIVATE – IS IT GROUPED WITH OTHER PEOPLE'S DNA REPORTS OR CAN I BE ID'd ??

Explosion of Genetic Testing Companies/Products

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- ▶ **Global Genetic Testing Market is set to exceed USD 22 billion by 2024;** according to a new research report by Global Market Insights.
- ▶ Innovation in genetic testing leading to enhanced efficiency, high sensitivity and safety will serve to be a high impact rendering factor.
- ▶ Technological advancement in scientific research as well as research instrument is increasing the importance of genetic testing.
- ▶ Availability of sensitive and efficient DNA sequencing technique for prenatal genetic testing allows detection of minute amount of DNA circulating in the mother's blood during early stages of pregnancy.
- ▶ Adoption of such non-invasive prenatal testing (NIPT) at a very early stage of pregnancy is increasing worldwide thereby augmenting the industry growth over the forecast period.
- ▶ Increasing applications of genetic testing for early detection and prevention of oncology and genetic diseases will accelerate the market growth throughout the forecast period.
- ▶ Around 6,00,920 cancer deaths occurred in the U.S. in 2017.
- ▶ Growing awareness among patients pertaining to early diagnosis of diseases will lead to timely treatment resulting in reduced mortality.
- ▶ Rising prevalence of diseases such as cancer, cystic fibrosis, Alzheimer's and other genetic diseases worldwide will result in increasing number of people undergoing genetic testing for early diagnosis thereby fueling the Genetic Testing Market growth.
- ▶ Request for a sample of this research report @ <https://www.gminsights.com/request-sample/detail/2490>

Explosion of Genetic Testing Companies/Products

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Global Genetic Testing Market is set to exceed USD 22 billion by 2024

Some of the notable industry players operating in global genetic testing market are; 23andMe, Abbott Molecular, Bayer Diagnostics, Biocartis, BioHelix, BioMerieux, BGI, Celera Genomics, Cepheid, Counsyl, deCODEme, Genentech, Genomictree, Genomic Health, HTG Molecular Diagnostics, IntegraGen, LabCorp Diagnostics, Luminex, MolecularMD, Myriad, Natera, PacBio, Pathway Genomics, Qiagen, Roche Diagnostics, Sequenom and Siemens.

Proliferation of Proprietary Multi-Gene Testing Panels

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- ▶ In the summer of 2013, the Supreme Court's decision in *Association for Molecular Pathology v. Myriad Genetics*¹ took a significant bite out of Myriad Genetics' patent portfolio. Now, almost a year later, the inexorable process of patent expiration is poised to take an even bigger bite.
- ▶ Myriad's thus-far proprietary VUS data would clearly satisfy this definition. The official commentary to UTSA provides that "reasonable use of a trade secret including controlled disclosure to employees and licensees is consistent with the requirement of relative secrecy."
- ▶ A number of stakeholder groups have made efforts to promote data sharing of genomic information. For example, the goal of comprehensive initiatives like the National Human Genome Research Institute's ("NHGRI") 1000 Genomes Project, The Human Gene Mutation Database in Wales, MutaDATABASE, and the Human Variome Project is to promote the creation of central databases of shared data about genetic variants so that the medical community can use this information to provide a "faster diagnosis, more accurate prognosis and ... better treatments"
- ▶ So, the fight goes on – can you claim ownership of a gene or gene product or database?
- ▶ Who will control these data in the future – will there be comprehensive sharing initiatives?
- ▶ Can companies share data or is it all for one and one for all from this day forward??

Does the FDA Regulate Gene Tests and Genetic Panels?



- ▶ Since 2017 the FDA began to regulate both genetic tests that are ordered from and performed at home (DTC) and those that are ordered from and performed in a healthcare setting or laboratory (a laboratory-developed test, or LDT). These two types of tests require different levels of FDA regulation.
- ▶ FDA WARNING: Genetic laboratory tests with claims to predict a patient's response to specific medications, that have not been reviewed by the FDA and may not be supported by clinical evidence. For example, genetic tests with claims to predict whether some medications used to treat depression may be less effective or have an increased chance of side effects.
- ▶ FDA WARNING: The FDA is alerting patients and health care providers that claims for many genetic tests to predict a patient's response to specific medications have not been reviewed by the FDA, and may not have the scientific or clinical evidence to support this use for most medications. Changing drug treatment based on the results from such a genetic test could lead to inappropriate treatment decisions and potentially serious health consequences for the patient.

Does the FDA Regulate Gene Tests and Genetic Panels?



- ▶ The FDA is looking into certain developers that may be inappropriately selling genetic tests for the unapproved uses noted above and will take compliance actions when appropriate, such as when the tests pose significant public health concerns.
- ▶ Following issuance of the safety communication, FDA reached out to several firms marketing pharmacogenetic tests with claims to predict how a person will respond to specific medications in cases where the relationship between genetic (DNA) variations and the medication's effects has not been established. Most firms addressed the FDA's concerns by removing specific medication names from their labeling, including promotional material and patient test reports.
- ▶ On April 4, 2019, the FDA issued a warning letter to Inova Genomics Laboratory, of Falls Church, VA, for illegally marketing genetic tests that claim to predict patients' responses to specific medications, also known as pharmacogenetics tests.
- ▶ The FDA will continue to monitor this issue and will keep the public informed if significant new information becomes available.

Does the FDA Regulate Gene Tests and Genetic Panels?



TABLE 1 Representative next generation sequencing-based gene panel tests

Panel test	No. of targeted genes	Enrichment approach	Tumor mutation burden	FDA approval	PMDA approval	References
OncoPrint Dx Target Test	23 genes	Amplicon	-	Yes	Yes	https://assets.thermofisher.com/TFS-Assets/LSG/brochures/oncomine-dx-target-test-flyer.pdf
MSK-IMPACT	468 genes	Capture	Yes	Yes	-	⁵⁶
FoundationOne CDx	324 genes	Capture	Yes	Yes	-	https://assets.ctfassets.net/vhriv12imne/6Rt6csmCPuaguuqmg12iY8/e3a9b0456e-d71a55d2e4480374695d95/FoundationOne_CDx.pdf
NCC Oncopanel	114 genes	Capture	-	-	-	https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000179757.pdf
Toda! OncoPanel	464 genes	Capture	-	-	-	http://todaioncopanel.lumin.jp/#sec01
CANCERPLEX	435 genes	Capture	Yes	-	-	⁵⁸
OncoPrime	223 genes	Unknown	-	-	-	⁷⁸
PleSision	160 genes	Unknown	-	-	-	http://www.hosp.keio.ac.jp/st/cancer/info/20180529_2.pdf
OmniSeq Advance	144 genes	Amplicon	Yes	-	-	⁷⁴
P5 report	52 genes	Unknown	-	-	-	http://www.okayama-u.ac.jp/user/hos/koganzai/P5report/

How To Standardize a Panel With Tens of Thousands of Base Pairs?

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- ▶ In general, three categories of genetic testing are available—cytogenetic testing, biochemical testing, and molecular testing—to detect abnormalities in chromosome structure, protein function and DNA sequence, respectively.
- ▶ Cytogenetic Testing - Cytogenetics involves the examination of chromosomes and their abnormalities. Chromosomes of a dividing human cell can be clearly analyzed in white blood cells, specifically T lymphocytes, which are easily collected from blood. Cells from other tissues such as bone marrow, amniotic fluid, and other tissue biopsies can also be cultured for cytogenetic analysis. Fluorescent in situ hybridization (FISH) is a process which vividly paints chromosomes or portions of chromosomes with fluorescent molecules to identify chromosomal abnormalities (e.g., insertions, deletions, translocations and amplifications).
- ▶ Biochemical Testing - Clinical testing for a biochemical disease utilizes techniques that examine the protein instead of the gene. Many biochemical genetic diseases are known as 'inborn errors of metabolism' since they are present at birth and disrupt a key metabolic pathway. Depending on the disease, tests can be developed to directly measure protein activity (enzymes), level of metabolites (indirect measurement of protein activity), and the size or quantity of protein (structural proteins). These tests require a tissue sample in which the protein is present, typically blood, urine, amniotic fluid, or cerebrospinal fluid. Because proteins are more unstable than DNA and can degrade quickly, the sample must be collected and stored properly and shipped promptly according to the laboratory's specifications.
- ▶ Molecular Testing - These tests require a tissue sample in which the protein is present, typically blood, urine, amniotic fluid, or cerebrospinal fluid. Because proteins are more unstable than DNA and can degrade quickly, the sample must be collected and stored properly and shipped promptly according to the laboratory's specifications. The amplified product can then be further tested, such as by digestion with a restriction enzyme and gel electrophoresis to detect the presence of a mutation/polymorphism.

Update on National Cancer Moonshot

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THE NATIONAL CANCER MOONSHOT INITIATIVE

The National Cancer Moonshot Initiative seeks to accelerate cancer research to make more therapies available to patients while also improving our ability to prevent cancer and detect it at an early stage.

The 21st Century Cures Act, passed in 2016, authorized \$1.8 billion over 7 years to fund the Cancer Moonshot. The same year, NCI convened a Blue Ribbon Panel (BRP) of many of the nation's top cancer experts - cancer researchers, oncologists, patient advocates, and private-sector leaders - to give careful thought to what could be done to expedite progress against cancer. To provide recommendations to the National Cancer Advisory Board, the BRP members collaborated with over 100 colleagues from across the cancer research community to identify 10 of the most compelling research opportunities poised for acceleration to help meet the goals of the Cancer Moonshot.

Implementation of the Moonshot is well under way, and over the past two fiscal years Congress has appropriated a total of \$600 million for the Cancer Moonshot, which has enabled NCI to support and accelerate research in each of the 10 areas recommended by the BRP. In fiscal year 2017 NCI received \$1 appropriation in May and was able to rapidly invest approximately \$277 million in new research opportunities before the end of the fiscal year. NCI issued 17 new Cancer Moonshot funding opportunities in fiscal year 2018 and is in the process of finalizing awards.

The Cancer Moonshot is providing the research community with new resources to pursue critical research questions and to build upon collaborations to ensure their success. These opportunities for acceleration were made possible by decades of investment in basic science and sustained support for the entire cancer research enterprise. Examples of new and ongoing Cancer Moonshot projects include:

- New adult and pediatric translational research immuno-oncology networks
- Improving the evidence-based follow-up care for individuals at high risk of cancer due to an inherited genetic susceptibility
- Generation of a detailed 3-dimensional map of cancer to inform future cancer research
- Creation of a basic and translational research consortium to focus on unique drivers of childhood cancers
- Innovative strategies to understand and combat tumor resistance to anticancer therapies
- Accelerating colorectal cancer screening and follow-up through multilevel interventions

NCI is currently planning new research opportunities for FY 2019 and beyond. For more information and updates, visit cancer.gov/moonshot

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NCI Match trial mutations & agents

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TABLE 2. Broadening Molecular Profiling Boundaries—Biomarker-Targeted Therapy Matches

TARGETED MUTATION	DRUG
NCI-MATCH trial: NCT02465060^a	
EGFR activating mutation	Atatinib
HER2 activating mutation	Atatinib
BRCA1 or BRCA2 mutations	Adavosertib (AZD1775)
TGFR pathway aberrations	AZD4547
NRAS12, NRAS13, NRAS61 mutation	Binimetinib
AKT mutation	Capivasertib (AZD 5363)
PIK3CA mutation	Copanlisib
PTEN mutation	Copanlisib
PTEN loss	Copanlisib
MET amplification	Crizotinib
MET exon 14 deletion	Crizotinib
ALK translocation	Crizotinib
ROS1 translocation or inversion	Crizotinib
BRAF V600E/V600R/V600K/V600D mutation	Dabrafenib + trametinib
DDR2 5768R, 1638F, or L239R mutation	Dasatinib
NF2 inactivating mutation	Defactinib
PTEN mutation or deletion and PTEN expression	GSK2636771 (PI3K inhibitor)
PTEN loss	GSK2636771 (PI3K inhibitor)
FGFR mutation or fusion	Erdafitinib
FGFR amplification	Erdafitinib
NTRK1, NTRK2, NTRK3 gene fusions	Larotrectinib (LOXO-101)
Loss of MSH1 or MSH2 (by IHC)	Nivolumab
EGFR T790M or rare activating mutation	Osimertinib
CCND1, CCND2, CCND3 amplification & Rb expression	Palbocicli
CDK4 or CDK6 amplification and Rb protein	Palbocicli
HER2 amplification ≥2 copy numbers	Pertuzumab + trastuzumab
TSC1 or TSC2 mutation	Sapanisertib
mTOR mutation	Sapanisertib
cKIT exon 9, 11, 13, or 14 mutation	Sunitinib
PIK3CA mutation	Tasefiob
CNAQ1/GNA11 mutation	Trametinib
BRAF fusion or BRAF non-V600 mutation	Trametinib
RAF1 mutation	Trametinib
HER2 amplification	Trastuzumab emtansine
SMO/PTCH1 mutation	Vismodegib

Molecular Testing for Solid Tumors 2019

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The Current State of Molecular Testing in the Treatment of Patients With Solid Tumors, 2019

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Abstract: The world of molecular profiling has undergone revolutionary changes over the last few years as knowledge, technology, and even standard clinical practice have evolved. Broad molecular profiling is now nearly essential for all patients with metastatic solid tumors. New agents have been approved based on molecular testing instead of tumor site of origin. Molecular profiling methodologies have likewise changed such that tests that were performed on patients a few years ago are no longer complete and possibly inaccurate today. As with all rapid change, medical providers can quickly fall behind or struggle to find up-to-date sources to ensure he or she provides optimum care. In this review, the authors provide the current state of the art for molecular profiling/precision medicine, practice standards, and a view into the future ahead. *CA Cancer J Clin* 2019;69:305-343. © 2019 The Authors. *CA A Cancer Journal for Clinicians* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Keywords: biomarkers, cancer, gene expression profiling, drug target, molecular-targeted therapy, molecular profiling, mutation, precision medicine, sequence analysis

- ▶ Includes the Current Recommendations for Biomarker/Molecular Testing for the Following Solid Tumors
- ▶ Can be Single Test or Molecular Profiling Assay
 - ▶ ANY Solid Tumor – Microsatellite Instability and Mismatch Repair Testing
 - ▶ Non-Small Cell Carcinoma of Lung
 - ▶ Colon and Rectum
 - ▶ Gastric, Esophageal and GE Junction
 - ▶ Pancreas
 - ▶ Prostate
 - ▶ Endometrial
 - ▶ Ovarian
 - ▶ Breast
 - ▶ Brain and Central Nervous System
 - ▶ Sarcoma
 - ▶ Head and Neck
 - ▶ Melanoma
 - ▶ Somatic Mutations that could also be Germline Mutations
 - ▶ And much more....

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TABLE 2. Broadening Molecular Profiling Boundaries—Biomarker-Targeted Therapy Matches

TARGETED MUTATION	DRUG
NCI-MATCH trial: NCT02456062*	
EGFR activating mutation	Atatinib
HER2 activating mutation	Atatinib
BRCA1 or BRCA2 mutations	Adavosertib (AD01773)
FGFR pathway alterations	AZD4547
NRAS/2, NRAS/3, HRAS/G1 mutation	Biomimab
AKT mutation	Capivasertib (AZD 5363)
PKC α mutation	Copanlisib
PTEN mutation	Copanlisib
PTEN loss	Copanlisib
MEF amplification	Crocinib
MYT exon 14 deletion	Crocinib
ALK translocation	Crocinib
ROS1 translocation or inversion	Crocinib
BRAF V600E/V600R/V600K/V600D mutation	Dabrafenib + trametinib
CDK2/3/5/6, 16/38, or L239R mutation	Dacatinib
MEP2 inactivating mutation	Dalpiciclib
PTEN mutation or deletion and PTEN expression	GSX2636771 (P3K) inhibitor
PTEN loss	GSX2636771 (P3K) inhibitor
FGFR mutation or fusion	Erdafitinib
FGFR amplification	Erdafitinib
ATR/1, ATR/2, ATR/3 gene fusions	Larotrectinib (LOXO-101)
Loss of MMR1 or MMR2 by H3	Nivolumab
EGFR T790M or rare activating mutation	Osimertinib
CCND1, CCND2, CCND3 amplification & Rb expression	Palbociclib
CDK4 or CDK6 amplification and Rb protein	Palbociclib
HER2 amplification ≥ 2 copy numbers	Perituzumab + trastuzumab
TSC1 or TSC2 mutation	Sapanisertib
in/OUT mutation	Sapanisertib
cKIT exon 9, 11, 13, or 14 mutation	Sunitinib
PKC α mutation	Tasitinib
GNAQ/GNA11 mutation	Trametinib
BRAF fusion or BRAF non-V600 mutation	Trametinib
MEP1 mutation	Trametinib
HER2 amplification	Trastuzumab emtansine
SMO/PFH1 mutation	Vismodegib

Molecular Testing for Solid Tumors 2020

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TABLE 1. Predictive Microsatellite Instability/Mismatch Repair Testing for Any Solid Tumor

BIOMARKER	TEST DETECTS	WHEN	TECHNOLOGY	RECOMMENDATIONS	EVIDENCE	CANCER TYPE
MMR	Expression	See <i>Microsatellite Instability-High Tumors and DNA Mismatch Repair</i> in the text	IHC	dMMR and MSI-H tests on available tissue are recommended to predict response to pembrolizumab ^a	Lower level, wide acceptance	All
MLH1, MSH2, MSH6, or PMS2	Mutation (= dMMR expression)		NGS	Where applicable, dMMR and MSI-H tests are used together to identify whether a patient should undergo further mutation testing for Lynch syndrome ^b		
MSI	Testing (changes in short repeated DNA sequences)	See <i>Microsatellite Instability-High Tumors and DNA Mismatch Repair</i> in the text	PCR, NGS	dMMR and MSI-H tests on available tissue are recommended to predict response to pembrolizumab ^a	Lower level, wide acceptance	All
				Where applicable, dMMR and MSI-H tests are used together to identify whether a patient should undergo further mutation testing for Lynch syndrome ^b		

Abbreviations: dMMR, deficient mismatch repair; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; PCR, polymerase chain reaction.

^aNivolumab alone or in combination with ipilimumab may also be an option for patients with colorectal cancer.

^bdMMR is a characteristic feature of Lynch syndrome, which can play a part in patients (particularly younger patients) with cancers of the gastrointestinal tract (particularly colorectal), endometrium, ovary, brain, breast, and renal pelvis. In Lynch syndrome, dMMR leads to insufficient repair of repetitive DNA sequences and thus a higher risk of multiple malignant tumors.

Molecular Testing for Solid Tumors 2020

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TABLE 2.1. Currently Recommended Molecular Testing for NSCLC

BIOMARKER	TEST DETECTS	WHEN	TECHNOLOGY	RECOMMENDATIONS	EVIDENCE	CANCER TYPE
ALK	Gene fusion	Metastatic workup	FISH, NGS, RT-PCR ^a	Response to oral ALK TKIs; alectinib has improved efficacy over crizotinib in first line	High-level, wide acceptance	Adenocarcinoma, large cell, NSCLC NOS
	Fusion protein expression	Together with EGFR testing in "never smokers" or small/mixed histology specimens	IHC ^b	Response to oral ALK TKIs, eg, crizotinib	Lower level, wide acceptance	Squamous cell
EGFR T790M	Mutation	Metastatic workup	NGS, multiple mutation testing	Resistant to EGFR TKIs	High-level, wide acceptance	Adenocarcinoma, large cell, NSCLC NOS
EGFR exon 21 (L858R, L861R), exon 20 (S760L), exon 18 (G719X, G719)	Mutation	Metastatic workup	NGS, multiple mutation testing	Sensitive to EGFR TKIs	High-level, wide acceptance	Adenocarcinoma, large cell, NSCLC NOS
EGFR exon 19	Deletion	Metastatic workup	NGS, multiple mutation testing	Sensitive to EGFR TKIs	Lower level, wide acceptance	Squamous cell
					High-level, wide acceptance	Adenocarcinoma, large cell, NSCLC NOS
EGFR exon 20 T792	Insertion/mutation	Metastatic workup	NGS, multiple mutation testing	Likely resistant to EGFR TKIs	Lower level, wide acceptance	Squamous cell
					High-level, wide acceptance	Adenocarcinoma, large cell, NSCLC NOS
ROS1	Fusion/rearrangement	Metastatic workup	NGS, FISH, RT-PCR	Responsive to ROS1 TKIs	Lower level, wide acceptance	Adenocarcinoma, large cell, squamous cell, NSCLC NOS
PD-L1	Protein expression ≥50%	Metastatic workup	NGS, multiple mutation testing	Response to pembrolizumab in first-line; FDA approved treatment ¹³	Lower level, wide acceptance	Adenocarcinoma, large cell, NSCLC, squamous cell NOS
KRAS	Mutation	Metastatic workup	Gene sequencing	Resistance to EGFR TKIs. Gives poor prognosis compared with KRAS wt	Lower level, wide acceptance	All NSCLC
BRAF	Mutation, V600E	Metastatic workup	NGS, pyrosequencing, AS-PCR	Emerging targeted agents ¹⁴ ; responsive to combined BRAF and MEK inhibition	Lower level, wide acceptance	All NSCLC
HER2	Mutation	Any time	NGS, multiple mutation testing	Emerging targeted agents ¹⁵	Lower level, limited acceptance	All NSCLC
MET	Amplification, mutation	Any time	NGS, FISH	Emerging targeted agents ¹⁶	Lower level, wide acceptance	All NSCLC
RET	Fusion, rearrangement	Any time	NGS, FISH, RT-PCR	Emerging targeted agents ^{17,18}	Lower level, wide acceptance	All NSCLC

Abbreviations: AS, PCR, allele-specific polymerase chain reaction; FDA, US Food and Drug Administration; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PD-L1, programmed death 1 ligand; RT-PCR, reverse transcription-polymerase chain reaction; TKIs, tyrosine kinase inhibitors; wt, wild type. ^aFISH is the US Food and Drug Administration-approved method for ALK gene rearrangement. NGS and RT-PCR currently are not used widely in clinical practice. ^bIHC can be used as a good alternative to FISH.¹⁴

Molecular Testing for Solid Tumors 2020

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TABLE 2. Currently Recommended Predictive Molecular Testing for Colon and Rectal Cancers

BIOMARKER	TEST DETECTS	WHEN	TECHNOLOGY	RECOMMENDATIONS	EVIDENCE	CANCER TYPE
<i>KRAS/NRAS</i> ^a	Mutation	Workup for metastatic disease (suspected or proven)	NGS ^b	Avoid cetuximab or panitumumab treatment in patients who have tumors with <i>KRAS</i> and <i>NRAS</i> mutations (exons 2, 3, and 4 in both)	NCCN indicate <i>lower level, wide acceptance</i> , but many believe classification is <i>high-level, wide acceptance</i>	Metastatic synchronous adenocarcinoma (any T, any N, M1), suspected or documented; or Metachronous metastases by CT, MRI, and/or biopsy, documented
<i>BRAF</i> ^a	Mutation V600E	Workup for metastatic disease (suspected or proven)	NGS, pyrosequencing, AS-PCR ^c	Cetuximab or panitumumab treatment is not recommended in patients who have tumors with <i>BRAF</i> V600E mutations unless given with a <i>BRAF</i> inhibitor such as vemurafenib The use of irinotecan in combination with cetuximab or panitumumab plus vemurafenib is recommended in all patients with previously treated mCRC.	NCCN indicates <i>lower level, wide acceptance</i> , but many believe classification is <i>high-level, wide acceptance</i>	Metastatic synchronous adenocarcinoma (any T, any N, M1), suspected or documented; or Metachronous metastases by CT, MRI, and/or biopsy, documented

Abbreviations: AS-PCR, allele-specific polymerase chain reaction; CT, computed tomography; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PCR, polymerase chain reaction.

^a*KRAS* and *NRAS* are determined alongside *BRAF* mutations.

^bTesting can be performed on primary and/or metastatic colorectal tissue specimens.

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TABLE 2. Currently Recommended Predictive Molecular Testing for Ovarian Cancers^a

BIOMARKER	TEST DETECTS	WHEN	TECHNOLOGY	RECOMMENDATIONS	EVIDENCE	CANCER TYPE
<i>BRCA1</i> and <i>BRCA2</i>	Mutation	Recurrent disease; initial workup if the patient has a strong family history on initial diagnosis	NGS	Include other homologous recombination pathway genes and MSI or DNA MMR; helps guide therapy (eg, PARP or other DDR enzyme inhibitors; chemotherapy response)	Lower level, wide acceptance	Ovarian cancer
<i>ATM</i>	Mutation	Recurrent disease; initial workup if the patient has a strong family history on initial diagnosis	NGS	Include other homologous recombination pathway genes and MSI or DNA MMR; helps guide therapy (eg, PARP or other DDR enzyme inhibitors; chemotherapy response)	Lower level, wide acceptance	Ovarian cancer
<i>BRIP1</i>	Mutation	Recurrent disease; initial workup if the patient has a strong family history on initial diagnosis	NGS	Include other homologous recombination pathway genes and MSI or DNA MMR; helps guide therapy (eg, PARP or other DDR enzyme inhibitors; chemotherapy response)	Lower level, wide acceptance	Ovarian cancer
<i>CHK2</i>	Mutation	Recurrent disease; initial workup if the patient has a strong family history on initial diagnosis	NGS	Include other homologous recombination pathway genes and MSI or DNA MMR; helps guide therapy (eg, PARP or other DDR enzyme inhibitors; chemotherapy response)	Lower level, wide acceptance	Ovarian cancer
<i>PALB2</i>	Mutation	Recurrent disease; initial workup if the patient has a strong family history on initial diagnosis	NGS	Include other homologous recombination pathway genes and MSI or DNA MMR; helps guide therapy (eg, PARP or other DDR enzyme inhibitors; chemotherapy response)	Lower level, wide acceptance	Ovarian cancer
<i>RAD51C</i> , <i>RAD51D</i>	Mutation	Recurrent disease; initial workup if the patient has a strong family history on initial diagnosis	NGS	Include other homologous recombination pathway genes and MSI or DNA MMR; helps guide therapy (eg, PARP or other DDR enzyme inhibitors; chemotherapy response)	Lower level, wide acceptance	Ovarian cancer

Abbreviations: DDR, DNA damage repair; MMR, mismatch repair; MSI, microsatellite instability; NGS, next-generation sequencing; PARP, poly (adenosine diphosphate-ribose) polymerase.

^aApproximately 25% of ovarian cancers have germline or somatic mutations in *BRCA1*-related or *BRCA2*-related genes, including *BRCA1*, *BRCA2*, *PALB2*, *BRIP1*, *RAO51C*, and *RAO51D*. These tumors are targetable by PARP inhibitors, but the US Food and Drug Administration recently extended the approval of the PARP inhibitors niraparib, rucaparib, and olaparib to patients who do not express these mutations.⁴⁵⁻⁴⁷

Resources

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- ▶ National Institutes of Health – nih.gov
- ▶ National Cancer Institute – cancer.gov
- ▶ National Cancer Institute – Match Trial
- ▶ National Cancer Institute – The Genetics of Cancer Series
- ▶ The National Cancer Moonshot Initiative
- ▶ National Human Genome Research Institute – genome.gov
- ▶ Genetic Information Nondiscrimination Act of 2008 (GINA ACT)
- ▶ Molecular Diagnostics in Cancer Tutorial – Research Advocacy Network
- ▶ Molecular Diagnostics in Clinical Oncology – Frontiers in Molecular Biosciences; doi: 10.3389/fmolb.2018.00076
- ▶ The Current State of Molecular Testing in the Treatment of Patients with Solid Tumors, 2019; CA CANCER J CLIN 2019;69-305-343
- ▶ <https://www.cancer.gov/news-events/cancer-currents-blog/2017/genomic-profiling-tests-cancer>
- ▶ Next Generation Sequencing-Based Gene Panel Tests for the Management of Solid Tumors; DOI: 10.1111/cas.13837; 16 October 2018; Wiley Cancer Science. 2019;110:6–15.
- ▶ Regulation of Genetic Tests - <https://www.genome.gov/about-genomics/policy-issues/Regulationof-Genetic-Tests>
- ▶ Genetic Test Availability And Spending: Where Are We Now? Where Are We Going? Health Aff (Millwood). 2018 May ; 37(5): 710–716. doi:10.1377/hlthaff.2017.1427. HHS Public Access
- ▶ Why Cancer Gene Variants are Frequently Reclassified - <https://www.cancernetwork.com/cancer-and-genetics/why-cancer-gene-variants-are-frequentlyreclassified>

So Many Questions

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