



Guide to Interpreting Genomic Reports: A Genomics Toolkit

A guide to genomic test results for
non-genetics providers

Created by the Practitioner Education Working
Group of the Clinical Sequencing Exploratory
Research (CSER) Consortium

Genomic Report Toolkit

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About this resource

This resource was created by a team of genomic testing experts. It is designed to help non-geneticist healthcare providers to understand genomic medicine and genome sequencing. The CSER Consortium¹ is an NIH-funded group exploring genomic testing in clinical settings.

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Key Points:

- The use of genomic tests (gene panels, exome sequencing, genome sequencing) is increasing in the clinical and research setting.
- An individual's genetic code contains millions of differences when compared to the human reference sequence. These differences, referred to here as variants are also sometimes called mutations.
- Genetic variants may be benign and have no impact or may be pathogenic and causative of disease. When it is unclear whether a variant has an impact it is referred to as a variant of uncertain significance.
- Genomic tests are often performed to make a diagnosis and explain symptoms. Results related to symptoms are called primary findings while results that are unrelated to symptoms are called secondary findings.
- Results of genomic testing may have medical and personal value to both the individual who underwent testing as well as his relatives.

This guide is intended for healthcare providers faced with understanding and interpreting their patients' genomic test reports. This guide is not intended to help select a test, but rather to help providers navigate test results.

Genetic Tests vs. Genomic Tests

Genetic testing allows for the identification of changes in chromosomes, genes, or proteins (a gene's encoded product). The results can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder.

While genetic testing has been performed for decades, over the past few years there has been a tremendous increase in the number and scope of genetic tests ordered due to improvements in technology and decreases in cost. Genomic tests that explore multiple genes (panels), most genes, and even tests that explore a person's entire genome, have become a reality. Yet, many healthcare providers have not been trained in how to understand the output of these increasingly common tests.

Next Generation Sequencing (NGS), used in diagnostic testing, generally involves determining the patient's genetic sequence in millions of short segments, called "reads" (each approximately 100 basepairs in length), assembling the reads into a complete sequence, then determining what genetic variants are present and interpreting what they mean.

Fragment



Sequence



Assemble



Next generation sequencing involves determining an individual's genetic sequence in millions of short segments which are then assembled into a complete sequence.

NGS is extremely flexible and has been implemented for sequencing only a few genes (e.g., hereditary breast cancer panels), **whole exomes** (all of the coding regions of DNA) or **whole genomes** (entire DNA sequence including both coding and noncoding regions).

NGS is now routinely performed in clinical diagnostic laboratories that perform genetic testing and are regulated by CAP and CLIA certifications. However, much is still unknown about when to use which kind of test (gene panels, exome testing, and genome testing), and for what clinical purpose. There are CPT codes for these new NGS tests, but insurance coverage is variable.

For exome or genome sequencing, potentially millions of **variants** are identified that differ between the patient and the "**reference sequence**" used for comparison. Most genetic variants have

little or no known impact on human health, so the variants must be filtered to identify the few that are medically meaningful. Genomic data from an individual's parents provides information that can help filter out benign genetic variants and identify **de novo** variants (variants that are not inherited). Generation of the sequence data, **variant calling**, and variant interpretation are all critical steps for providing accurate test results.

Genomic testing is often done for an individual patient (**singleton**) or for a **trio** (includes patient, mother, and father); however other formats are possible depending on the disease of interest and family structure. Not all laboratories handle the testing and interpretation of parental samples in the same way. In some labs all three individuals are sequenced and interpreted comprehensively at the same time. In other labs the parental samples are only tested after the patient's sample.

Making sense of genetic variation

Individual genetic variants are classified by the testing laboratory, to indicate whether the laboratory believes a variant to be disease causing (**pathogenic**) and how certain this assessment is. Laboratories often use a 5-point scale to assign pathogenicity from **benign** (not disease causing) to pathogenic, with intervening scores of likely benign, **variant of uncertain significance**, and likely pathogenic. The American College of Medical Genetics and Genomics (ACMG) has published guidelines for laboratories to use in their interpretation and scoring of genetic variation². However, laboratories will vary in the types of variants they report. Some laboratories may report only pathogenic and likely pathogenic variants while others may report variants of uncertain significance as well. Laboratories typically do not report benign or likely benign findings. Sometimes variants that are associated with causing disease are also called **mutations**. *To reduce confusion, all genetic changes—whether they cause a medical condition or have no impact at all—are now called variants.*



Genomic variants are typically classified on a five-point scale to indicate the likelihood that the particular variant is associated with disease.

Genomic tests such as exome or genome sequencing can provide different kinds of information. Results that are directly related to explaining a patient's symptoms or reason for testing are often called **primary findings**, while results that are medically meaningful but unrelated to the reason for testing are often called secondary or incidental findings. When using genomic testing to diagnose patient symptoms, examples of **secondary findings** may include genetic risks for future disease, carrier status (carrying a gene for, but not exhibiting, a condition), and pharmacogenomics findings (findings related to differences in how a person may process medications). Often laboratories request information about what kinds of secondary findings a patient would like reported during the test ordering and informed consent process. Laboratories vary in how these choices are categorized and structured.

At this time there is also wide variability among genomic laboratories in the scope and structure of their result reports. During the development of this toolkit that authors reviewed information from several different labs to help providers make sense of the language they will see in these reports.

Limitations

There are limitations to genomic testing using NGS. A “negative” test report does not exclude the possibility of an underlying genetic disease. There may also be variants of uncertain significance reported that will become better understood over time. Additionally, several types of genetic variants are not robustly detected by NGS methods. The sensitivity of the test is disease specific and should be considered before ordering.

It is highly likely that a genetic variant reported is truly present, particularly if the laboratory uses a second testing method (such as **Sanger sequencing**) to confirm this. However, it is more difficult to determine the *significance* of a variant. Laboratories do their best to accurately label genetic variants as pathogenic or likely pathogenic, but a classification may be incorrect. Further, emerging evidence may lead to reclassification. The original report would then have been a **false positive**.

Should family members be tested?

Genomic test results may provide information about potential genetic variants and risk factors among a patient’s family members. When a genetic variant is identified in an individual, it is important to determine whether relatives are at risk of also having that genetic change and what follow-up testing might be indicated.

What about genetic discrimination?

Many patients may have questions about who will have access to their test results and how that information can be used. *Genetic discrimination* refers to using a person’s genetic information (test results, family history) against him or her in a harmful way. The Genetic Information Nondiscrimination Act (GINA), a federal law passed in 2008, largely protects against genetic discrimination in the areas of health insurance and employment. However, this legislation does not apply to life, disability, and long-term care insurance. To learn more about GINA, visit <http://ginahelp.org/>. Individual states may have additional laws that protect against genetic discrimination.

About this toolkit

This toolkit is organized into different sections, based on the different categories of results that may be generated by a genomic test. Each category includes example results and the benefits, limitations, and special considerations associated with each category.

References:

1. Green, R.C., et al. “Clinical Sequencing Exploratory Research Consortium: Accelerating Evidence-Based Practice of Genomic Medicine.” *Am J Hum Genet.* 2016 Jun 2;98(6):1051-66.
2. Richards, S. et al. “Standards and Guidelines for Interpretation of Sequence Variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and Association for Molecular Pathology.” *Genetics in Medicine.* 2015 17: 405-423.

Resources:

ClinGen (<http://clinicalgenome.org>): a NIH-funded resource that defines the clinical relevance of genes and variants for use in medicine and research.

ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>): a public archive of reports about the relationship between specific genetic variants and associated phenotype (symptoms).

GeneReviews (<http://www.ncbi.nlm.nih.gov/books/NBK11116/>): a collection of chapters, each focused on an individual genetic condition or disease, written for healthcare providers by experts in the field.

GINA (<http://www.ginahelp.org/>): an online resource about genetic discrimination and the Genetic Information Nondiscrimination Act.

National Society of Genetic Counselors (<http://nsgc.org/>): the professional organization for genetic counselors, with patient and provider resources and a searchable tool to “find a genetic counselor” near you.

OMIM (<http://www.ncbi.nlm.nih.gov/omim>): an online resource about human genes and associated phenotype (symptoms).

Key Points:

- Pathogenic variants in disease genes related to phenotype (or symptoms) means that a cause of the patient's symptoms has been identified.
- Clinically, both pathogenic and likely pathogenic variants are treated the same—as if they are likely disease causing.



Genomic variants are typically classified on a five-point scale to indicate the likelihood that the particular variant is associated with disease.

Often when a **whole exome** or **whole genome** sequence test is performed, the primary goal is to answer a diagnostic question about a patient with a specific set of symptoms (**phenotype**). When a genetic cause is identified that is believed to account for the symptoms, the result is described as a **primary finding** with one or more “**pathogenic**” or “**likely pathogenic**” variants in disease genes related to the phenotype. In other words, there is an answer and a definitive or highly probable cause to return to the patient and provider.

If the particular **variant** found has been previously associated with the condition, the variant will be classified as “pathogenic.” However, frequently, there is insufficient evidence that a variant is the definite cause for symptoms. The term “likely pathogenic” means that the variant most likely has a harmful effect. When a gene is associated with a disease that overlaps with the patient's symptoms, it then represents the likely diagnosis and cause. Sometimes, the gene has been linked to disease and the clinical features of the condition overlap with the patient's symptoms, but the exact gene variant identified in the patient has not been previously observed, making interpretation difficult.

Many factors are considered in assessing whether a variant is pathogenic. Clinically, pathogenic and likely pathogenic variants are usually treated the same—as if they are likely disease causing—and clinical management is tailored based on this diagnosis.

Example:

A patient presents with vision loss, obesity, renal failure, and cognitive deficits. Genomic sequencing identifies a variant in the BBS10 gene. The BBS10 gene is associated with Bardet-Biedl syndrome and is consistent with all of the clinical features in the patient. In addition, the specific variant has been repeatedly described in the literature in patients diagnosed with Bardet-Biedl syndrome. Based on this evidence, the variant would be classified as pathogenic. In contrast, if sequencing identified a different variant in BBS10 that had not been previously observed in either healthy or symptomatic populations, the variant would probably be classified as “likely pathogenic.” With time and as more individuals are sequenced, many “likely pathogenic” variants are reclassified to “pathogenic.”

Next Steps to Consider:

- Learn more about the condition with which the patient has been diagnosed through GeneReviews and other resources
- Referral to genetic services (medical geneticist and/or genetic counselor) for medical follow-up and discussion of recurrence risks and implications for other family members
- Identification of relevant patient support groups and resources specific to diagnosis
- Identification of relevant research studies or clinical trials specific to diagnosis

Resources

ClinicalTrials.gov (<https://clinicaltrials.gov/>): a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

GeneReviews (<https://www.ncbi.nlm.nih.gov/books/NBK1116/>): a resource for clinicians that provide clinically relevant and medically actionable information for inherited condition. This resource includes information on diagnostic criteria, management, and information about genetic counseling for patients and their families. There are chapters available about many, but not all, genetic conditions.

National Society of Genetic Counselors (<http://nsgc.org/>): the professional organization for genetic counselors, with patient and provider resources and a searchable tool to “find a genetic counselor” near you.

Key Points:

- Variants of Uncertain significance have an uncertain relationship to disease.
- It is not recommended that Variants of Uncertain Significance be used for clinical decision making.
- International efforts are underway to reclassify VUS variants as benign or pathogenic.
- Finding a VUS is common among large-scale tests like gene panels, whole exome, and whole genome sequencing.



Genomic variants are typically classified on a five-point scale to indicate the likelihood that the particular variant is associated with disease.

Sequencing of a gene can identify variants that are different from the reference sequence, yet not well understood. In contrast to genetic variants that have been confirmed to be associated with increased risk for developing a disease, a **Variant of Uncertain Significance (VUS)** has an uncertain relationship to disease.

There are several reasons why variants are classified as VUS, such as:

- a. The effect of the specific genetic alteration on gene function is not known.
- b. There are insufficient genetic data to definitively confirm that the variant is associated with risk of developing the disease.
- c. The patient is unaffected and has no symptoms, or different symptoms than those expected based on the variant found.

As more data accumulate over time, a VUS may be reclassified to likely pathogenic or likely benign. Until a VUS is reclassified, clinicians are advised not to use a VUS result for clinical decision-making. Further, the American College of Medical Genetics and Genomics (ACMG) recommends against using a VUS result for genetic testing in at-risk relatives because the meaning of the result is uncertain¹. However, testing of certain relatives can sometimes provide useful data to the testing laboratory to aid in the eventual reclassification of the variant.

International efforts are underway to systematically review all genomic variants, with the objective of reclassifying VUS results according to best practice guidelines. Many clinical genetic testing laboratories will, as a matter of policy, issue an amended report when a VUS result is reclassified to a category considered clinically actionable, and these amended reports are usually sent to the physician who ordered the test. As reclassification of a VUS may occur years after the original test was performed, clinicians and patients may consider re-contacting the laboratory that performed the genetic testing periodically for updates. In addition, resources are available online that enable clinicians to explore variants identified in their patients. For example, ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>) is a robust online resource that catalogues the classification of specific genetic variants, submitted by genetic testing laboratories and experts.

In the case of genetic tests that examine multiple genes, such as multigene panels, whole exome sequencing, and whole genome sequencing, the likelihood of finding one or more VUS is high; some studies report VUS in as many as 1 in 3 patients². Individuals undergoing multigene sequencing tests should receive pre-test education about the fact that such testing increases the likelihood of a VUS result. In addition, patients of a non-Caucasian ethnic background that has been less well characterized have an increased likelihood of VUS results.

Example:

A 39-year-old woman diagnosed with breast cancer undergoes gene sequencing for alterations in the *BRCA1* and *BRCA2* genes and is found to carry a variant of uncertain significance (VUS) in *BRCA2*. Two years later, the woman is diagnosed with another cancer - a sarcoma. She undergoes genomic sequencing of both tumor DNA and germline DNA (healthy, non-tumor DNA). Her germline DNA result shows a pathogenic variant (or mutation) in the *TP53* gene, a well-known tumor suppressor gene associated with Li Fraumeni syndrome. This new information confirms a diagnosis of Li Fraumeni, a hereditary cancer syndrome characterized by strikingly increased rates of cancer, in this patient.

Further review of data on the initial *BRCA2* variant shows that this variant is now known to be commonly observed in individuals of Asian ancestry and has been reported in 5 individuals who were also confirmed to carry pathogenic mutations in other cancer-associated genes. As a result, the *BRCA2* variant is reclassified as “likely benign.”

The initial genetic test identified a VUS in *BRCA2*. Although *BRCA2* is one of the most common genes implicated in breast cancer, the variant was classified as a VUS because of insufficient information. The fact that a pathogenic germline mutation in *TP53* was subsequently identified in this patient helped confirm that the *BRCA2* VUS was likely benign. This woman’s



family members should be offered testing for the pathogenic *TP53* variant to help assess their cancer risk. Had testing for the *BRCA2* VUS been offered to the family members their test results would have been misleading, since it is the germline *TP53* pathogenic variant, not the *BRCA2* VUS, that is responsible for the increased cancer risk in this family.

Next Steps to Consider

- Referral to genetic services (medical geneticist and/or genetic counselor) for medical evaluation and in-depth discussion of the identified genetic variant
- Contact the testing laboratory periodically for reanalysis of the genetic variant to determine whether more is known about its disease association
- Explore current knowledge about the specific genetic variant utilizing resources such as ClinVar
- Identification of relevant research studies specific to the gene or variant identified
- Consider periodic reanalysis of genomic test data as knowledge and databases used in analysis improves over time

Resources:

ClinicalTrials.gov (<https://clinicaltrials.gov/>): a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>): a public archive of reports about the relationship between specific genetic variants and associated phenotype (symptoms).

National Society of Genetic Counselors (<http://nsgc.org/>): the professional organization for genetic counselors, with patient and provider resources and a searchable tool to “find a genetic counselor” near you.

References:

1. Richards S. et al. Standards and Guidelines for Interpretation of Sequence Variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and Association for Molecular Pathology. *Genetics in Medicine* (2015); 17: 405-423.
2. Domchek, S. Multiplex Genetic Testing for Cancer Susceptibility: Out on the High Wire without a net? *J Clin. Oncol.* 2013; 31: 1267-70.

Key Points:

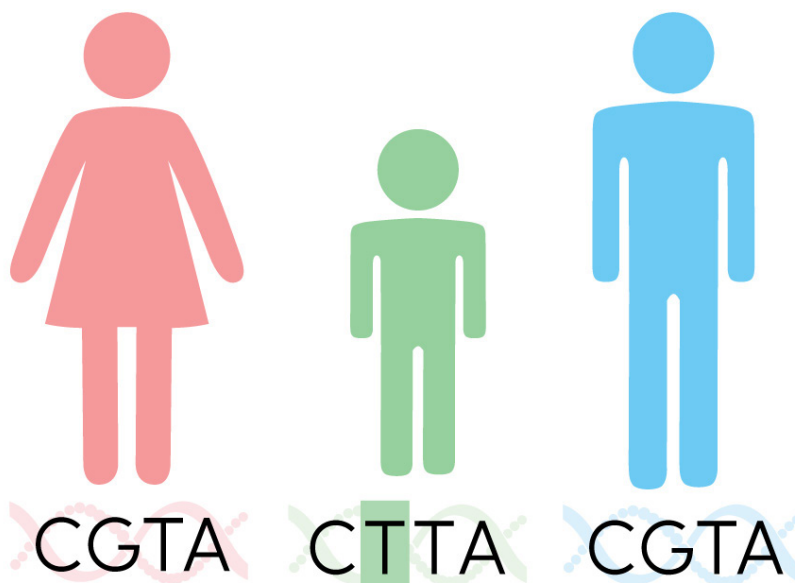
- A negative (normal) result reduces but does not eliminate the possibility that there is a genetic cause for the patient's condition.
- Whole genome sequencing may identify genetic causes missed by whole exome sequencing.
- With time, more variants will be recognized as disease causing and reanalysis of whole exome or whole genome data may be helpful in the future.

With **whole exome** or **whole genome sequencing**, when a genetic cause is not identified that is believed to account for the patient's symptoms (phenotype), the result is described as "normal" or "negative" or "none detected" for mutations in disease genes related to **phenotype**. In other words, there is no answer and there is no identifiable genetic cause for the patient. A normal result reduces but does not eliminate the possibility that there is a genetic cause for the patient's condition. Rather, it indicates that a genetic cause could not be identified.

The limitations of the test should be reviewed with the patient. There are important reasons why a genetic cause may not be identified by whole exome or whole genome sequencing. Whole exome sequencing only captures and sequences 1-2% of the genome, and the disease causing variants could be in **non-coding DNA regions** that are not targeted for capture or in coding regions that are not well captured by the test.

On average, more than 95% of most genes are captured with current technology, but coverage varies by the lab, capture kit, and by gene. The disease causing variant may have been captured and sequenced, but it may be part of a gene that is not yet associated with disease. The disease causing variant may have been sequenced and may be present in a known disease causing gene but may be a **novel** variant that was not understood to be disease causing. While laboratories can sequence whole exomes and genomes, there are limitations in the technology and the interpretation of the data that may allow for a disease-causing genetic change to be missed. Additional limitations include certain kinds of genetic changes that are not easily detected through sequence based methods, including **repeat expansions** and structural chromosome rearrangements. It is important to make sure any genes of particular interest were adequately interrogated by the chosen test. A negative genomic test does not rule out a genetic cause for disease.

Sequencing a **trio**, meaning a patient and both of his or her biological parents, can increase the diagnostic yield as it allows the laboratory to identify variants that are **de novo** (not inherited). If only the affected individual was sequenced, such variants are less likely to be interpreted correctly and less likely to be reported.



Sequencing an individual as well as both biological parents can increase diagnostic yield as it allows for the identification of de novo (not inherited) variation.

Next Steps to Consider:

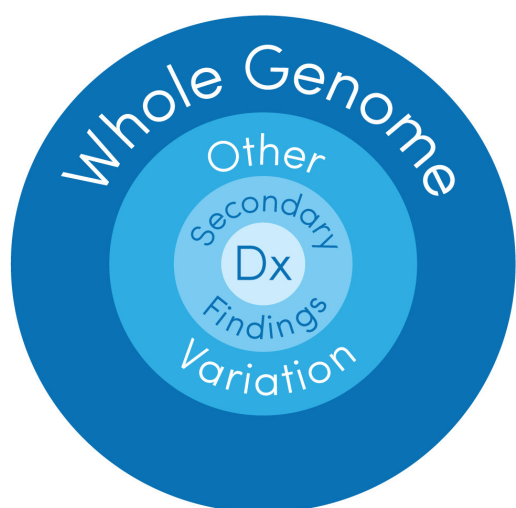
- Referral to genetic services (medical geneticist and/or genetic counselor) for medical evaluation and/or additional testing that may supplement the genomic test
- Consider other types of diagnostic testing for the patient as the cause of symptoms or reason for testing has not yet been explained
- Consider periodic reanalysis of genomic test data as knowledge and databases used in analysis improves over time

Resources

National Society of Genetic Counselors (<http://nsgc.org/>): the professional organization for genetic counselors, with patient and provider resources and a searchable tool to “find a genetic counselor” near you.

Key Points:

- Secondary findings are additional results that do not directly relate to the reason for testing.
- Patients are often given the opportunity to opt in/out of receiving secondary findings when a whole exome or genome sequencing is ordered.
- Common types of secondary findings include risk of future disease, response to medications, and carrier status results.
- Many laboratories only report secondary findings that are medically actionable.



Genomic sequencing is used to aid in the diagnosis of a patient who, because of symptoms or family history, is suspected to have an underlying genetic disorder. The term “**secondary findings**” refers to results that do not pertain to this primary diagnostic question. Secondary findings are a diverse category. Some secondary findings are **medically actionable**, meaning they prompt clinical action by the patient’s medical provider. In the case where genomic sequencing is being performed to identify future disease risk in an ostensibly healthy individual, results that are traditionally thought of as secondary findings may become the primary findings.

The terms “secondary findings” and “**incidental findings**” are often used interchangeably; however, they are sometimes employed in different ways. The secondary findings label is applied to results that are unrelated to the diagnostic question, but are nonetheless systematically sought out and analyzed. Incidental findings are *not* sought out, but identified nonetheless. Other terms that have been used to refer to secondary findings include “additional findings,” “off-target results,” and “unanticipated findings.”

Secondary findings, if present, are typically reported for the person undergoing sequencing. When exome sequencing is completed for relatives of that person, such as parents for trio analysis, secondary findings may also be reported in relatives.

Example:

A patient presents with a personal history of peripheral neuropathy. Genomic sequencing is performed and a pathogenic variant is identified in the *MLH1* gene. Pathogenic mutations in the *MLH1* gene are associated with hereditary Lynch syndrome, which increases an individual's risk to develop a variety of cancers including colon cancer. However, it is unrelated to the neuropathy symptoms and would thus not be part of the patient's diagnostic result. This result would be classified as a secondary finding, unrelated to symptoms and reason for testing. Patients with Lynch syndrome are advised to have a colonoscopy with removal of any polyps every 1-2 years beginning in their mid-20s. This is a highly effective way to reduce colon cancer risk in individuals with Lynch syndrome. Because the identification of a pathogenic *MLH1* mutation would prompt the patient's clinician to initiate the colonoscopy screening protocol at the appropriate age, this is a medically actionable secondary finding.

Genomic testing can identify risk factors for future disease development. Genomic testing can also provide information about an individual's **carrier status** for **autosomal recessive** diseases. While carrier status is not expected to impact an individual's own health or medical care and is not actionable in the same way as was the secondary finding in the example above, it may be considered medically actionable by some, particularly by patients of reproductive age and their providers. Similarly, **pharmacogenomics** results (results concerning how genes affect a person's response to drugs) may be included in secondary findings. These results would be medically actionable only if the patient takes a relevant drug. For more information about these types of results, please see Section 7: Pharmacogenomics Results.

How likely is a medically actionable secondary finding?

Most, if not all, laboratories offering clinical genomic sequencing return medically actionable secondary findings of some sort. The likelihood of such a finding depends on how secondary findings are defined and analyzed by the laboratory. The **American College of Medical Genetics and Genomics (ACMG)** proposed a list of 56 genes with 24 associated **phenotypes** as a minimum list of secondary findings to be systematically analyzed and reported by laboratories offering exome or genome sequencing¹. It has been estimated that ~1% of patients undergoing exome sequencing would receive a secondary finding using this list.

Because it would be inappropriate to initiate medical intervention for an unaffected person on the basis of uncertain information, laboratories typically only report pathogenic or **likely pathogenic** variants as secondary findings². The ancestral background of the patient undergoing sequencing may influence the likelihood of a secondary finding. To date, individuals of European Caucasian ancestry have been overrepresented among cohorts undergoing genetic sequencing. Thus, there

may be more evidence available to assess pathogenic and likely pathogenic variants in this group. Causative variants identified in non-European Caucasian populations such as African or Asian may go unrecognized due to lack of data, may be labeled **variants of uncertain significance (VUS)**, or may not be reported.

Depending on a specific laboratory's policy, there is often an opportunity for patients to opt in or out of receiving such secondary findings.

What if there are no medically actionable secondary findings?

Most patients undergoing genomic sequencing will not have a medically actionable secondary finding. This means there were no genetic variants identified that suggested a high likelihood of an actionable genetic condition that was unanticipated due to clinical signs and symptoms. Laboratories set a high bar for returning secondary finding results. Therefore, a lack of medically actionable secondary findings is not a clean bill of health, and does not reduce a person's risk for future health problems such as cancer, cardiac arrhythmia, or vascular disease, since in the general population, most cases of such health problems are not attributable to the types of rare genetic conditions revealed as secondary findings from genetic sequencing. In addition, **false negative** results are possible due to a number of technological and interpretive limitations. Secondary findings must be examined in the context of the individual's medical history and family history.

Why might a lab report secondary findings that are not medically actionable?

Many laboratories only report secondary findings that are not medically actionable if the patient actively chooses to receive such information. However, some laboratories may report on secondary findings that are not medically actionable but may be highly predictive. For example, pathogenic mutations in the *SOD1* gene are associated with familial amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. People with a pathogenic mutation in this gene have a 90% chance to develop ALS by the time they are in their 70s. This finding would not be considered medically actionable because there are currently no therapies to prevent or delay ALS, or slow its progress. Despite this, a result of this sort may be desired. Patients electing to learn this type of information should consider possible benefits (such as enhanced ability to plan) with possible negative consequences (such as the risk of life insurance discrimination, or increased anxiety).

Age Matters

Most laboratories that return medically actionable secondary findings routinely do so regardless of the age of the patient. Laboratories that offer non-medically actionable secondary findings generally offer this only for adults who are competent to provide informed consent to receive this category of findings.

References:

1. Green, R. C., et al. "ACMG Recommendations for Reporting Incidental Findings in Clinical Exome and Genome Sequencing." *Genet Med*. 2013 Apr;15(7):565-574. https://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf
2. Amendola, L.M., et al. "Actionable exomic incidental findings in 6503 participants: challenges of variant classification." *Genome Res*. 2015 Mar;25(3):305-15.

Resources:

Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts, from the Presidential Commission for the Study of Bioethical Issues http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf

Key Points:

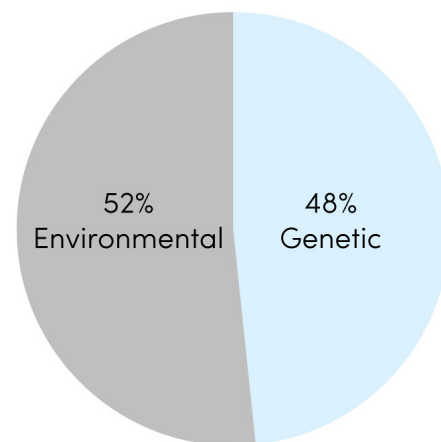
- Common complex disorders such as heart disease, diabetes, and most cancers develop as a result of both genetic and environmental factors.
- The association of a common risk allele with disease is often modest, as is its impact on clinical care.
- Interpretation of common risk alleles for clinical management can be challenging.

Differences in the DNA sequence at a specific location in a gene are called variants, or alleles. Alleles with a high population frequency, typically defined as $>1\%$, are referred to as **polymorphisms**. These small differences in DNA sequence, or genetic variation, may or may not affect gene function. However, some common variants can interfere with a biological process, leading to illness, typically in combination with other factors. Such conditions are considered to have a genetic basis, and are typically classified as “common complex” disorders.

In contrast to Mendelian disorders (e.g. Huntington’s disease, sickle cell anemia) in which variation in a single gene causes disease, common complex disorders, such as heart disease, diabetes, and most cancers, develop as a result of both genetic and environmental factors. Because common complex diseases can be associated with alterations in many different genes, and because each of these alterations is usually associated with only small increases in risk, the finding of a common risk allele has much less impact on clinical care than finding a gene mutation associated with a Mendelian disorder.

Risk alleles for common complex diseases are usually defined by the **minor**, or *least* common, **allele frequency** (MAF). This allows for differentiation between common and rare alleles in the population. The MAF of common risk alleles can range from 5% to 50%. However, just because an allele is common does not necessarily mean it has a meaningful impact on disease susceptibility.

Coronary Artery Disease Heritability Chart



Common complex disorders, such as coronary artery disease, develop as a result of multiple genetic and environmental factors.

Common risk alleles are often detected by **genome-wide association studies** (GWAS)^{1,2}. GWAS are a type of case-control study in which people with the condition being studied are compared to similar people without the condition. Each person's complete set of DNA, or genome, is surveyed by examining a strategically selected "panel" of genetic markers that tag areas of known variation, called **single nucleotide polymorphisms** (SNPs).

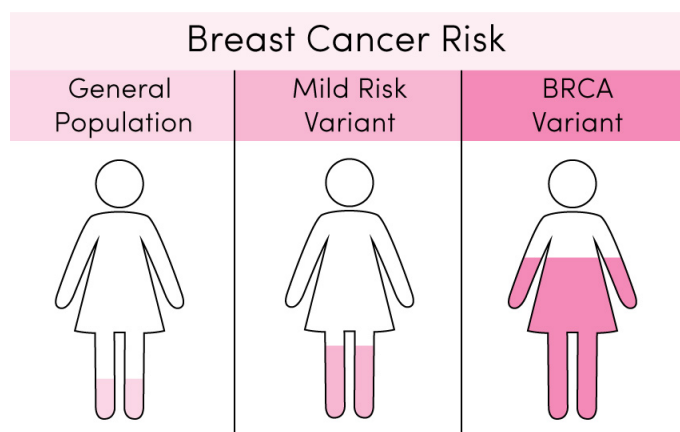
If certain genetic variations are found to be more frequent in people with the disease compared to people without disease, the variant alleles are said to be "**associated**" with the disease. The presence of an association suggests that the variant, or some other nearby variant, is influencing disease susceptibility.

The association of an allele with disease is a measure of statistical, not clinical significance. Effects are often modest, and the associated variants themselves may not directly cause the disease. Given this, genetic tests for such conditions can only provide an estimate of probability or risk. For common diseases, the presence of a high-risk allele may only mildly increase the chance of disease. Further, there are currently no validated ways of combining multiple risk alleles for the same disease. These limitations can make the interpretation of common risk alleles challenging.

Examples:

One risk allele that is relatively common in the population and that has been associated with an increased risk for disease susceptibility is factor V Leiden and risk for deep venous thrombosis (DVT). Between 3- 8% of people of European descent carry one copy of the factor V Leiden allele and 1 in 5,000 people have two copies. Risk of DVT for individuals in the general population is 1 in 1,000. However, having one copy of the factor V Leiden allele increases the risk of DVT from 1 in 1,000 to 3-8 in 1,000. Having two copies raises the risk to as high as 80 in 1,000. A test that identifies the factor V Leiden allele can have implications for clinical management and may indicate the need for preventative measures to reduce clotting risk².

In contrast, variants in the *MTHFR* gene have been associated with increased risk of neural tube defects and cardiovascular disease; however, 60-70% of individuals in the general population have one of the two most common *MTHFR* gene polymorphisms. Most of these individuals do not develop disease. Therefore, a genetic test that identifies one of these *MTHFR* gene variants has no real clinical implications.



The average woman in the United States has about a 1 in 8, or 12% chance of developing breast cancer during her lifetime. Genetic variants in highly penetrant genes (*BRCA1* and *BRCA2*) confer a significantly higher risk of being diagnosed with breast cancer, while changes in other genes have a more moderate impact on risk.

In the case of breast cancer, several alleles that increase susceptibility have been identified. Pathogenic mutations in the *BRCA1* and *BRCA2* genes associated with the Mendelian disorder Hereditary Breast and Ovarian Cancer Syndrome are associated with lifetime risks for breast cancer of 40-80%. In contrast, more than 70 other common alleles have been associated with breast cancer susceptibility, most of which confer only a mild to moderate increase in risk. Thus, identifying one of these common alleles would not have the same implications for medical management as would finding a pathogenic mutation in *BRCA1* or *BRCA2*. To what extent the associated symptoms are expressed in the presence of the variant is captured by a term called **penetrance**. If it is not always expressed, it is considered incompletely penetrant.

If an associated allele is identified, it may explain disease susceptibility. Common risk alleles with a known association with a condition can inform an individual of an increased or decreased risk of developing the condition in question; however, the degree of certainty is often unknown. The presence of a common risk allele can indicate a need for increased surveillance, while a negative result implies a risk similar to the general population.

Common risk alleles have unclear implications for family members. In addition, the clinical **sensitivity** of tests for common risk alleles is not necessarily high. Common complex diseases are caused by multiple genetic and environmental factors, many of which remain unknown.

References:

1. Hirschhorn, J.N., Lohmueller, K., Byrne, E., Hirschhorn, K. "A comprehensive review of genetic association studies." *Genet Med*. 2002 Mar-Apr;4(2):45-61.
2. Raychaudhuri, S. "Mapping rare and common causal alleles for complex human diseases." *Cell*. 2011 Sep 30;147(1):57-69.
3. Geerts, W.H., et al. "Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)." *Chest*. 2008;133(6_{suppl}):381S-453S.

Next Steps to Consider

- Use of risk allele information to guide medical management is rarely done in the absence of a practice guideline
- Explore current knowledge about the specific genetic variant utilizing resources such as the medical literature, professional guidelines and NHGRI GWAS catalog
- In most cases, testing of family members is not recommended apart from a specific practice guideline

Resources:

dbSNP (<https://www.ncbi.nlm.nih.gov/projects/SNP/>;) a public-domain archive for a broad collection of simple genetic polymorphisms.

Human Genome Variation (HGV) database (<http://www.nature.com/hgv/>): a searchable online database of genome variations published in a variety of peer-reviewed sources. HGV is searchable and able to be filtered by different variables, including specific disease, gene, population or region.

Iles, M.M. 2008. "What can genome-wide association studies tell us about the genetics of common disease?" PLoS Genet. 2008 Feb;4(2):e33.

OMIM (<http://www.ncbi.nlm.nih.gov/omim/>): an online resource about human genes and associated phenotype (symptoms).

Vineis P., Schulte, P., McMichael, A.J.. "Misconceptions about the use of genetic tests in populations." Lancet. 2001 Mar 3;357(9257):709-12.

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2. Raychaudhuri, S. "Mapping rare and common causal alleles for complex human diseases." Cell. 2011 Sep 30;147(1):57-69.
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Key Points:

- A carrier is usually asymptomatic due to having one working and one non-working copy of a gene.
- There is typically a risk for an affected child when both parents are carriers of the same genetic variant.
- Carrier status can be discovered in various clinical testing scenarios; testing may be ordered specifically looking for carrier status for reproductive planning or to diagnose a symptomatic individual.

A **carrier** is an individual who has one working and one non-working copy of a gene. A carrier is capable of passing on a **genetic variant** associated with recessive disease (**autosomal recessive** or **x-linked recessive**) to their offspring. A carrier usually does not display disease symptoms associated with that variant, although in some rare cases a carrier might exhibit some symptoms.

In an individual with a recessive disease, both copies of the gene have variants associated with disease. Autosomal recessive diseases are typically not seen in every generation of an affected family and are equally likely to occur in males and females. **One example of an autosomal recessive disease is cystic fibrosis.** Both parents of an individual with an autosomal recessive disease likely carry one copy of the altered gene.

Females have two X chromosomes, and males have one X and one Y chromosome. For X-linked conditions, women are typically carriers and have fewer if any symptoms, while males are affected. Males are at an increased risk of disease because they only have one copy of the X chromosome and therefore only one copy of the many genes located on the X chromosome. If one of these genes is not working, there is not another copy to compensate.

A female carrier for an X-linked recessive disease has a 50% chance of passing on the variant in each pregnancy. Sons that inherit the variant would be expected to be affected with the condition, while daughters with the variant are less likely to exhibit symptoms. **An example of an X-linked recessive disease is Hemophilia A.** A male with an X-linked condition will pass on the variant to each of his daughters (because the variant is on his X chromosome, which he passes on to each female child) and none of his sons (because each son receives only a Y chromosome from his father).

Carrier status can be discovered in a variety of clinical testing scenarios. Tests may be ordered specifically looking for carrier status, identifying people who carry one copy of a gene variant that can be

passed on to a child. This type of testing is currently offered to individuals who have a family history of a genetic disease, people in certain ethnic groups with an increased risk of specific genetic diseases (population screening), and people concerned about their risk of having a child with a genetic disease.

All individuals are carriers of multiple genetic diseases. However, rarely are partners having a child both carriers for the same autosomal recessive condition. If couples undergo carrier screening, the test results can provide information about their risk of having a child with a genetic disease. In this scenario the carrier status would be considered a **primary result**, as it is related to the reason the test was ordered. Carrier testing can be ordered in various ways, including targeted single gene disease testing, panel testing of multiple genetic diseases, or less commonly through a broad genomic test looking for genetic variants throughout the genome or exome.

Carrier status information can be used for reproductive planning and may provide information to other relatives about a possible shared genetic variant. In rare cases when carriers can exhibit symptoms, a carrier result could inform medical management for the individual being tested.

Example:

A woman has preconception genome sequencing to plan for a future pregnancy. She is found to be a carrier of a pathogenic mutation for cystic fibrosis. Her husband then has genetic testing to see if he is a carrier of the same mutation. He is negative, meaning a cystic fibrosis associated variant was not identified. Based on these results, this couple are very unlikely to have a child with the condition. However children will have a 50% chance of being an unaffected carrier like their mother.

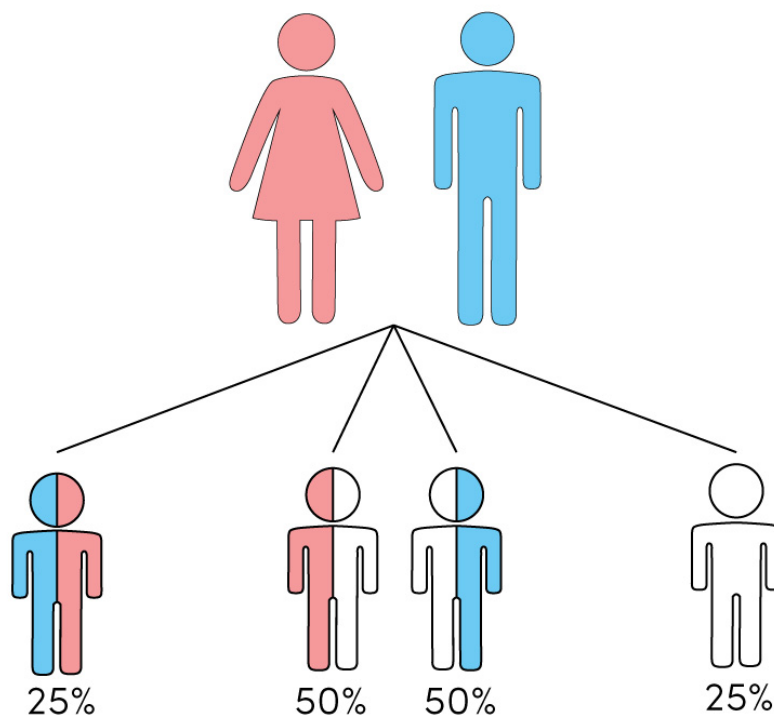
Carrier status can also be revealed as a **secondary finding**, or incidental finding when the primary testing indication is for another reason (e.g., diagnosis of a symptomatic individual) that is unrelated to assessing carrier status. In this case the carrier result may be relevant to the patient, siblings, parents, or other relatives for future reproductive planning. As above, in some rare cases in which carriers exhibit symptoms, a carrier result could inform medical management.

Limitations

There are some important limitations to be aware of when interpreting carrier results from a genomic test. Carrier testing is a screening test. If one has a negative carrier test result, there is still a residual risk of being a carrier due to the possibility of a genetic variant that was not detected or reported. Sequencing does not identify all types of variants. This limitation means that the most

common variants for some well-known and commonly tested for diseases such as spinal muscular atrophy (SMA) and Fragile X are cannot reliably be detected by NGS. In addition, many laboratories do not routinely report **variants of uncertain significance** (VUS) related to carrier status results. An individual may still be a carrier of (or affected with) a disease if no variants or only one variant is found in the relevant gene.

Some variants (and associated genetic diseases) are more common in certain ethnic groups, due to a single genetic variant or set of common genetic variants within that population. However, variants in all genes can occur in any population. It is important to note whether a test interrogates a set of common variants, or sequences entire genes (and identifies both common and rare variants). This, as well as the **carrier frequency** within the patient's specific population group, is important when determining risk related to a negative result.



A carrier for a recessive condition is asymptomatic and has a pathogenic genetic variant in just one of their two copies of the associated gene. Parents that are both carriers of the same recessive condition have a 25% chance that a child will inherit the pathogenic variant from both parents and be affected with the condition. There is a 50% chance that the child will inherit a single pathogenic variant from one parent and will also be an asymptomatic carrier. There is a 25% chance that the child will inherit neither variant and will not be affected or a carrier.

Next Steps to Consider:

- Learn more about the recessive condition with which the patient has been diagnosed through GeneReviews, OMIM and other resources
- Referral to genetic services (medical geneticist and/or genetic counselor) for in-depth discussion of reproductive risks and implications for family members
- Carrier testing of patient's partner for the specific gene/genetic condition identified to further clarify risk of having a child with the recessive disorder

Resources:

GeneReviews (<https://www.ncbi.nlm.nih.gov/books/NBK1116/>): a resource for clinicians that provide clinically relevant and medically actionable information for inherited condition. This resource includes information on diagnostic criteria, management, and information about genetic counseling for patients and their families. There are chapters available about many, but not all, genetic conditions.

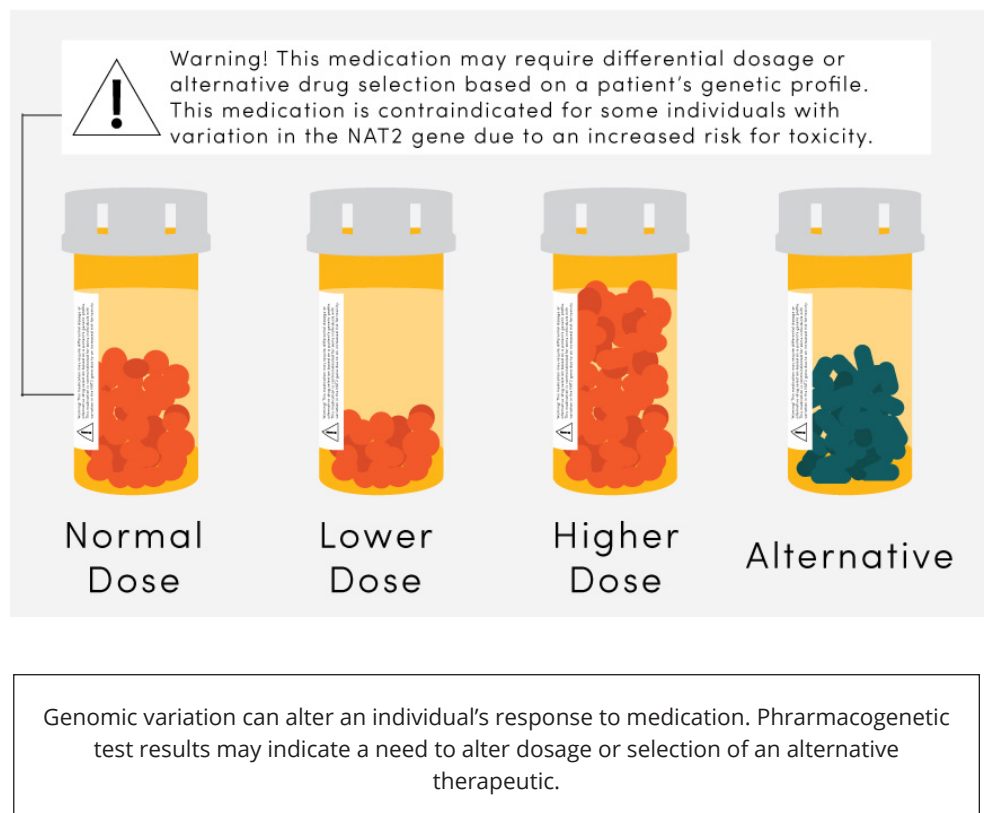
National Society of Genetic Counselors (<http://nsgc.org/>): the professional organization for genetic counselors, with patient and provider resources and a searchable tool to "find a genetic counselor" near you.

Key Points:

- Pharmacogenetic information can play an important role in identifying individuals at risk for reduced therapeutic response or at risk for **toxicity** when given normal doses of particular medications.
- A comprehensive table of medications and their pharmacogenomic biomarker labeling information is available for FDA approved medications.
- Gene-drug guidelines to help prescribers with drug selection and dosing can be found at <https://cpicpgx.org/>

Pharmacogenetic results from exome or whole genome sequencing refer to genetic variants associated with differential *responses to medications*. These genetic variants may result in variable rates of medication clearance or metabolism. Certain variants may increase a patient's immune response to a medication. Pharmacogenetics results can alert providers to a patient's risk for reduced or absent therapeutic response, or to possible toxicity-related adverse events. These can be prevented with medication choice, dose adjustments, or both.

Variation within the CYP2C9 gene alters metabolism of many commonly used medications including warfarin and valproic acid. HLA gene variants may cause a patient to have severe adverse reactions when taking certain medications such as carbamazepine. To learn more about specific gene-drug interactions visit PharmGKB (<https://www.pharmgkb.org/>).



Example:

The **American College of Medical Genetics and Genomics (ACMG)** has proposed a list of 56 genes which should be explored as part of secondary analysis when clinical exome or genome sequencing is conducted. One is the *RYR1* gene. Some pathogenic variants in *RYR1* have been shown to increase susceptibility to malignant hyperthermia when halothane gases, used as a general anesthetic, or succinylcholine, a short-acting muscle relaxant, are administered. Malignant hyperthermia can cause a fast and potentially fatal rise in body temperature and severe muscle contractions. Individuals known to have an increased susceptibility to this reaction because of pathogenic variants in *RYR1* should be given alternative medications when undergoing general anesthesia.

Many researchers are studying the return of pharmacogenetic results to the patient's Electronic Medical Record (EMR) when exome or whole genome sequencing is used. Therefore, clinical sequence data may be analyzed in the relatively near future for important drug response variants associated with professional guidelines or recommendations.

Using pharmacogenomics information to inform medication selection, dosing or both may reduce risk for adverse drug reactions. Consideration of a patient's other current medications or medical conditions that inhibit or induce genetically normal or differential processes are essential, in addition to consideration of differential drug response due to genetic variants. A comprehensive table of medications and their pharmacogenomic labeling information is available for FDA approved medications:

<http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>

Next Steps to Consider

- Consider currently prescribed medications in light of pharmacogenomic results
- Consult pharmacogenomic results as new medications are being considered and prescribed
- Explore current knowledge about the specific genetic variant(s) utilizing resources such as CPIC and PharmGKB

Resources:

PharmGKB (<https://www.pharmgkb.org>) - PharmGKB is a NIH funded pharmacogenomics resource developed by Stanford University that seeks to aid researchers in understanding how genetic variation contributes to differences in drug reactions.

Clinical Pharmacogenetics Implementation Consortium (CPIC) (<http://cpicpgx.org/>) - CPIC creates and publishes peer-reviewed guidelines for the implementation of pharmacogenetic information into medical practice.



While a patient's DNA sequence will not change over time, our understanding of his or her sequence will change, especially given our improving knowledge of genomics and disease. With time, more variants will be recognized as disease causing and our understanding of currently identified variants may change. Reanalysis of patient exome or whole genome data may be appropriate in the future.

This toolkit and its resources are meant to provide an introduction to genomic testing for non-genetics healthcare providers. While this guide is certainly not "the final word" on these kinds of test results, as the field is changing so rapidly, we believe it will provide useful guidance in understanding the results of today's tests.



Autosomal recessive: genetic conditions that occur only when mutations are present in both copies of a given gene (i.e., the person is homozygous for a mutation, or carries two different mutations of the same gene, a state referred to as compound heterozygosity).

[Source – NCI Dictionary of Genetics Terms]

Benign (variant): an alteration in a gene distinct from the normal, wild-type allele that does.

[Source – Illustrated Glossary]

Carrier frequency: the proportion of individuals in a population who have a single copy of a specific recessive gene mutation; also sometimes applied to the prevalence of mutations in dominantly acting genes such as BRCA1 and BRCA2. Also called carrier rate.

[Source – NCI Dictionary of Genetics Terms]

Carrier: an individual who has a recessive, disease-causing variant at a particular location on one chromosome of a pair and a typically functioning allele at that location on the other chromosome.

[Source – CSER Consortium Practitioner Education Working Group]

Clinical sensitivity: the frequency with which a test yields a true positive result among individuals who actually have the disease or the gene mutation in question. A test with high sensitivity has a low false-negative rate and thus does a good job of correctly identifying affected individuals.

[Source – NCI Dictionary of Genetics Terms]

De novo (variant): an alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents, or a mutation that arises in the fertilized egg itself during early embryogenesis. Also called a new mutation.

[Source – NCI Dictionary of Genetics Terms]

Exome: the exome is the small subset (1-2%) of an individual's entire genetic sequence, or genome, that directly instructs the building of a particular protein. Although a small fraction of the genome, the exome includes the sequence of approximately ~22,000 genes.

[Source – CSER Consortium Practitioner Education Working Group]

False negative: a test result which indicates that an individual is unaffected and/or does not have a particular gene mutation (variant) when he or she is actually affected and/or does have a gene mutation (variant); i.e., a negative test result in an affected individual.

[Source – Illustrated Glossary]



False positive: a test result which indicates that an individual is affected and/or has a certain gene mutation (variant) when he or she is actually unaffected and/or does not have the mutation (variant); i.e., a positive test result in a truly unaffected individual.

[Source – Illustrated Glossary]

Genetic variant: a change in the DNA sequence as compared to a reference sequence that may or may not have an impact on protein function or disease state. Terms such as mutation and polymorphism have been largely replaced by ‘variant’ to simplify terminology.

[Source – CSER Consortium Practitioner Education Working Group]

Genome: the entire set of genetic instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes, found in the nucleus, as well as a small chromosome found in the cells’ mitochondria. Each set of 23 chromosomes contains approximately 3.1 billion bases of DNA sequence.

[Source – Talking Glossary of Genetic Terms]

Genome-wide association studies: a genome-wide association study (GWAS) is an approach used in genetics research to associate specific genetic variations with particular diseases. The method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of a disease.

[Source – Talking Glossary of Genetic Terms]

Likely pathogenic variant: a DNA change that is most likely causing a deleterious effect on an encoded protein product that accounts for the observed symptoms.

[Source – CSER Consortium Practitioner Education Working Group]

Medically actionable: used to alter the treatment or surveillance of a patient.

[Source – CSER Consortium Practitioner Education Working Group]

Next generation sequencing: a high-throughput method used to determine a portion of the nucleotide sequence of an individual’s genome. This technique utilizes DNA sequencing technologies that are capable of processing multiple DNA sequences in parallel. Also called massively parallel sequencing and NGS.

[Source – NCI Dictionary of Genetics Terms]



Novel variant: a newly discovered, distinct genetic alteration; NOT the same as new or de novo variant (or mutation). Also called novel mutation.

[Source – NCI Dictionary of Genetics Terms]

Pathogenic: a genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder. When such a variant (or mutation) is inherited, development of symptoms is more likely, but not certain. Also called deleterious mutation, disease-causing mutation, predisposing mutation, and susceptibility gene.

[Source – NCI Dictionary of Genetics Terms]

Penetrance: a characteristic of a genotype; it refers to the likelihood that a clinical condition will occur when a particular genotype is present.

[Source – NCI Dictionary of Genetics Terms]

Pharmacogenomics: a branch of pharmacology concerned with using DNA and amino acid sequence data to inform drug development and testing. An important application of pharmacogenomics is correlating individual genetic variation with drug responses.

[Source – Talking Glossary of Genetic Terms]

Phenotype: the observable characteristics in an individual resulting from the expression of genes; the clinical presentation of an individual with a particular genotype.

[Source – NCI Dictionary of Genetics Terms]

Polymorphism: a common mutation. "Common" is typically defined as an allele frequency of at least 1%. All genes occur in pairs, except when x and y chromosomes are paired in males; thus a polymorphism with an allele frequency of 1% would be found in about 2% of the population, with most carriers having one copy of the polymorphism and one copy of the normal allele.

[Source – NCI Dictionary of Genetics Terms]

Primary result: alterations in a gene or genes that are relevant to the diagnostic indication for which the test was ordered.

[Source – CSER Consortium Practitioner Education Working Group]

Reference sequence: the 'standard' sequence of DNA for a particular organism that is used to compare new sequence data against for alignment and identification of variation.

[Source – CSER Consortium Practitioner Education Working Group]



Repeat expansion: Some areas within the human genome contain small repetitive sequences of DNA (i.e. CAG). The number of repeats at a particular genomic location is typically stable. However, an increase in repeat number has been associated with several human diseases such as Huntington Disease and Fragile X syndrome.

[Source – CSER Consortium Practitioner Education Working Group]

Sanger sequencing: a low-throughput method used to determine a portion of the nucleotide sequence of an individual's genome. This technique uses polymerase chain reaction (PCR) amplification of genetic regions of interest followed by sequencing of PCR products.

[Source – NCI Dictionary of Genetics Terms]

Secondary result: refers to genomic test results that do not pertain to the primary diagnostic question or reason for testing. Also referred to as an incidental finding.

[Source – CSER Consortium Practitioner Education Working Group]

Single nucleotide polymorphism: DNA sequence variation that occurs when a single nucleotide (adenine, thymine, cytosine, or guanine) in the genome sequence is altered; usually present in at least 1% of the population. Also called SNP.

[Source – NCI Dictionary of Genetics Terms]

Singleton: typically used to refer to the sequencing of one individual rather than a family unit.

[Source – CSER Consortium Practitioner Education Working Group]

Toxicity: the dosage at which a drug causes adverse effects within the body.

[Source – CSER Consortium Practitioner Education Working Group]

Trio: typically refers to the sequencing and analysis of an affected individual as well as his or her mother and father.

[Source – CSER Consortium Practitioner Education Working Group]

Variant calling: the process of comparing a DNA sequence of interest to a reference.

[Source – CSER Consortium Practitioner Education Working Group]

Variant of uncertain significance: A variant of uncertain significance is a change in the DNA sequence whose association with disease is unknown. Also called a variant of unknown significance, unclassified variant, or sometimes simply a VUS.

[Source – CSER Consortium Practitioner Education Working Group]



X-linked recessive: a mode of inheritance in which a mutation (variant) in a gene on the X chromosome causes the phenotype (symptoms) to be expressed in males who are hemizygous for the gene mutation (i.e., they have only one X chromosome) and in females who are homozygous for the gene mutation (i.e., they have a copy of the gene mutation on each of their two X chromosomes). Carrier females who have only one copy of the mutation do not usually express the phenotype, although differences in X-chromosome inactivation can lead to varying degrees of clinical expression in carrier females.

[Source – Illustrated Glossary]

