UNIT 8 - GENETIC TESTING

Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev

Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

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Attribution

8.1 UNIT OVERVIEW

Learning Objectives

- Describe different types and applications of genetic testing
- Discuss ethical and legal protections for genetic testing
- Examine the role of the nurse in working with patient's receiving genetic testing
- Review genomic variant classification

Outline

Topics covered in this chapter include:

- Genetic testing overview
- Types of Genetic tests
- Genetic tests validity and reliability
- Interpreting genetic test results

Competencies Nurses will Develop in this Chapter

ANA (2023):

Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).

Identification:

- Identifies credible, accurate, appropriate, and current genomic information, resources, services, and technologies specific to given clients.
- Recognizes issues that undermine the rights of all clients for autonomous, informed genomic-related decision-making and voluntary action.

Provision of education, care, and support:

- Facilitates clients' access to credible, accurate, appropriate, and current genomic information, resources, services, and technologies.
- Advocates for autonomous, informed genomic-related decision-making.
- Demonstrates in practice the importance of tailoring genomic information and services that are responsive to the unique attributes of every person.

Provision of education, care, and support:

- Performs interventions appropriate to clients' genomic health care needs.

NHS (2023):

Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the key indicators of a potential genetic condition, or clinical situation where genomics-informed healthcare would be appropriate;
- recognizing the importance of family history in assessing predisposition to a genetic condition; and
- taking appropriate and timely action to seek assistance from and refer individuals to genomics specialists, other specialists and peer support resources.

Demonstrate effective communication in tailoring genomic information and services to the individual:

- recognizing factors (such as ethnicity, culture, religion, ethical values, developmental stage or language) that may influence the individual's ability to use information and services.

Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

Apply knowledge, understanding and context of genomic testing and information to underpin care and support for individuals and families prior to, during and following decision-making:

- including types, uses and limitations of genomic tests to prevent, predict or treat a health condition, and an awareness of the processes for testing and return of results;
- recognizing that decision-making and testing in some situations may be time-critical;
- incorporating awareness of the ethical, legal and social issues related to testing, recording, sharing and storage of genomic information and data; and
- incorporating awareness of the potential physical, emotional, psychological and social consequences of genomic information for individuals, family members and communities.

Examine your own competency of practice on a regular basis:

- based on an understanding of the boundaries of your professional role in delivering genomic healthcare including the referral, provision or follow-up to genomic services.

Obtain and communicate reliable, current information about genomics, for self, patients, families and colleagues:

- using information technologies and other information sources effectively to do so; and
- applying critical appraisal skills to assess the quality of information accessed.

Provide ongoing nursing care and support to patients, carers, families and communities with genomic healthcare needs:

- demonstrating awareness about how a genomic test result can have implications for family members and might impact on family dynamics.

Key terminology

Analytical validity

How well a test predicts the presence or absence of a particular gene or genetic change (Medline, 2024).

Carrier screening

Carrier screening involves testing to see if a person “carries” a genetic variation (allele) associated with a specific disease or trait. A carrier has inherited a normal and a variant allele for a disease- or trait-

associated gene, one from each parent. Most typically, carrier screening is performed to look for recessively inherited diseases when the suspected carrier has no symptoms of the disease, but that person's offspring could have the disease if the other parent is a carrier of a harmful variant in the same gene.

Expanded carrier screening refers to reproductive genetic carrier screening beyond one's ethnicity and family history (GECKO, 2024).

Chromosomal tests:

These tests analyze whole chromosomes or long lengths of DNA to identify large-scale changes, such as an extra or missing copy of a chromosome (trisomy or monosomy, respectively) or abnormalities of large segments of chromosomes, that underlie certain genetic conditions (Medline, 2021a).

Clinical validity

How well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease (Medline, 2024).

Clinical utility

Whether the test can provide helpful information about diagnosis, treatment, management, or prevention of a disease (Medline, 2024).

Direct-to-consumer testing

Genetic testing that can be ordered by any individual; it is not a clinical test therefore does not need to be ordered by a medical professional.

Exome

An exome is the sequence of all the exons in a genome, reflecting the protein-coding portion of a genome. In humans, the exome is about 1.5% of the genome.

Molecular gene tests:

These tests determine the order of DNA building blocks (nucleotides) in an individual's genetic code, a process called DNA sequencing. The purpose of these tests is to identify pathogenic genetic variants (Medline, 2021a).

Multigene panels

Look for variants in many genes in the same test (Medline, 2021a).

Newborn screening

Used to test babies one or two days after birth to find out if they have certain diseases known to cause problems with health and development (NHGRI, 2019).

Next-generation DNA sequencing

DNA sequencing establishes the order of the bases that make up DNA. Next-generation DNA sequencing (abbreviated NGS) refers to the use of technologies for sequencing DNA that became available shortly after the completion of the Human Genome Project (which relied on the first-generation method of Sanger sequencing). Faster and cheaper than their predecessors, NGS technologies can sequence an entire human genome in a single day and for less than 1,000.

Pharmacogenomic testing

Provides information about how certain medicines are processed by an individual's body (NHGRI, 2019).

Predictive/pre-symptomatic genetic test

Used to find gene changes that increase a person's likelihood of developing diseases. The results of these tests provide information about the risk of developing a specific disease. Such information may be useful in decisions about lifestyle and healthcare (NHGRI, 2019).

Prenatal screening

Is offered during pregnancy to help identify fetuses that have certain diseases (NHGRI, 2019).

Reproductive genetic carrier screening

Facilitates informed decision-making by future parents through identifying those couples at increased risk of having an affected child with a serious genetic disorder (autosomal or X-linked recessive) (GECKO, 2024).

Research genetic testing

Used to learn more about the contributions of genes to health and to disease (NHGRI, 2019).

Sanger sequencing

A method of DNA sequencing that involves electrophoresis and is based on the random incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication. After first being developed by Frederick Sanger and colleagues in 1977, it became the most widely used sequencing method for approximately 40 years (Wikipedia, 2024).

Screening (genetic)

Used in people who do not have signs or symptoms of a disorder. These tests estimate whether an individual's risk of having a certain condition is increased or decreased compared with the risk in other people in a similar population (Medline, 2021a).

Single gene tests

Look for variants in only one gene (monogenic disorder) (Medline, 2021a).

Whole exome sequencing

Looks at all the genes in the DNA (whole exome) or just the genes that are related to medical conditions (clinical exome) (Medline, 2021b).

Whole genome sequencing

Looks at all of a person's DNA, not just the genes (Medline, 2021b).

Attribution & References

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8.2 GENETIC TESTING OVERVIEW

What is genetic testing?

Genetic testing is a type of medical test that looks for changes in DNA. Genetic tests analyze cells or tissue to look for changes in genes, chromosomes, and proteins.

Genetic testing may be done for many different reasons:

Predictive and **pre-symptomatic** genetic tests are used to find gene changes that increase a person's likelihood of developing diseases. The results of these tests provide information about the risk of developing a specific disease. Such information may be useful in decisions about lifestyle and healthcare.

Carrier testing is used to find people who "carry" gene variants linked to disease. Carriers may show no signs of the disease. However, they can pass on the gene change to their children, who may develop the disease or become carriers themselves. Some diseases require a gene change to be inherited from both parents for the disease to occur. This type of testing is usually offered to people who have a family history of a specific inherited disease or who belong to certain ethnic groups that have a higher risk of specific inherited diseases.

Prenatal testing is offered during pregnancy to help identify fetuses that have certain diseases. This type of testing is offered during pregnancy if there is an increased risk that the baby will have a genetic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them make decisions about a pregnancy. However, it cannot identify all possible inherited disorders and congenital disabilities.

Newborn screening is used to test babies one or two days after birth to determine if they have certain diseases that cause health and development problems.

Pharmacogenomic testing gives information about how an individual's body processes certain medicines. This type of testing can help healthcare providers choose the drugs that work best with an individual's genetic makeup.

Research genetic testing is used to learn more about the contributions of genes to health and disease. Sometimes, the results may not be directly helpful to participants, but they may benefit others by helping researchers expand their understanding of the human body, health, and disease.

What are the benefits of genetic testing?

Genetic testing may be beneficial whether the test identifies a variant or not. Test results are a relief for some people, eliminating some uncertainty surrounding their health. These results may also help doctors make recommendations for treatment or monitoring and give people more information for making decisions about

their and their family's health, allowing them to take steps to lower their chance of developing a disease. For example, as a result of such a finding, someone could be screened earlier and more frequently for the disease and could change health habits like diet and exercise. Such a genetic test result can lower a person's feelings of uncertainty, and this information can also help people make informed choices about their future, such as whether to have a baby.

What are the risks and limitations of genetic testing?

The physical risks associated with most genetic tests are minimal, particularly for those tests that require only a blood sample or buccal smear. The procedures used for prenatal diagnostic testing carry a small but real risk of miscarriage because they require a sample of amniotic fluid or tissue from around the fetus.

Many of the risks associated with genetic testing involve the results' emotional, social, or financial consequences. Genetic testing can cost anywhere from less than $100 to more than $2,000. Health insurance companies may cover part or all of the cost of testing.

People may feel angry, depressed, anxious, or guilty about their results. Because family members share DNA, some family members may have the same variants. For this reason, in some cases, genetic testing creates tension within a family.

Genetic testing can provide only limited information about an inherited condition. The test often can't determine if a person will show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. Another major limitation is the lack of treatment strategies for many genetic disorders once they are diagnosed.

The possibility of genetic discrimination in employment or insurance is also a concern. This will be explored in greater detail in chapter 10.2.

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8.3 TYPES OF GENETIC TESTS

How are genetic screening tests different from genetic diagnostic tests?

Screening tests evaluate an individual's *risk* of developing a genetic condition, while diagnostic tests identify genetic conditions. All genetic tests have both benefits and limitations.

Genetic **screening tests** are generally used in people who do not have signs or symptoms of a disorder. These tests estimate whether an individual's risk of having a certain condition is increased or decreased compared with the risk in other people in a similar population. A positive result means that a person's risk of developing the condition is higher than average. A negative screening test means that a person's risk is lower than average. However, *having a positive screening result does not mean the individual has the condition.* Because screening tests are only estimates, the results, in some cases, indicate an increased risk for a genetic abnormality when the person is unaffected (false positive), or the results indicate a decreased risk for a genetic abnormality when the person is affected (false negative). While genetic screening tests do not provide a conclusive answer, they can help guide the following steps, such as whether additional diagnostic testing is needed.

Genetic **diagnostic tests** are often used in people who have signs and symptoms. These tests are used to *confirm or rule out suspected genetic conditions*. Diagnostic tests can also help inform a person's chance of developing a genetic condition or passing it to their children. Diagnostic testing can be performed before birth or at any time during a person's life, but it is not available for all genes or all genetic conditions. The results of a diagnostic test can be used to guide a person's choices about health care and the management of the disorder.

Concept in Action

Watch Genetic Testing's Impact on Patient Care – Page's Story (4 mins) on YouTube (https://youtu.be/-UHg0oEqdAg) to learn how genetic testing can impact a patient's diagnostic odyssey.

How are genetic tests performed?

Genetic tests are performed on a sample of blood, hair, skin, amniotic fluid (the fluid that surrounds a fetus during pregnancy), or other tissue. For example, a buccal (pronounced buh-kl (https://dictionary.cambridge.org/pronunciation/english/buccal#google_vignette)) smear uses a small brush or cotton swab to collect a sample of cells from the inside surface of the cheek. Depending on the suspected disorder, the sample is sent to a laboratory where technicians look for genetic variants in chromosomes, DNA, or proteins. If requested, the laboratory reports the test results in writing to a person's doctor, genetic counsellor, or patient. Before a person has a genetic test, it is important to obtain informed consent to be sure they understand the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results. The International Society of Nurses in Genetics (ISONG) has a position statement on informed decision-making related to genetic testing and the nurse's role [PDF] (https://www.isong.org/resources/Documents/Informed%20decision%20making%20position%20statement%20approved%20Dec%202018.pdf).

Examples of genetic screening tests

Reproductive genetic carrier screening Carrier screening supports informed decision-making for prospective parents by identifying couples at higher risk of having a child affected by a severe genetic condition, whether autosomal or X-linked recessive (Henneman et al., 2016; Plantinga et al., 2016; Yao et al., 2016). The optimal time to discuss carrier screening is during the preconception period, when individuals are planning pregnancy, or at a woman's first prenatal visit, regardless of gestational age (Edwards et al., 2015; Wilson et al., 2016). Current Canadian and international guidelines recommend offering carrier screening based on an individual's ethnic background or the presence of specific personal or family history risk factors (Edwards et al., 2015; Henneman et al., 2016; Wilson et al., 2016). Canadian recommendations for Point of Care tools (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/expanded-carrier-screening/point-of-care-tool-9) on reproductive genetic screening are available. "**Expanded carrier screening** refers to reproductive genetic carrier screening beyond one's ethnicity and family history" (GECKO, n.d.-d).

Noninvasive prenatal testing/screening (NIPT/NIPS): This screening test is performed before birth to help determine the risk that a fetus will be born with certain genetic abnormalities, such as Down syndrome and other chromosomal disorders (MedlinePlus, n.d.-a).

For more information, see GECKO *on the run:* Non-invasive prenatal testing (NIPT) (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/non-invasive-prenatal-testing/gecko-on-the-run-10) – a 2-page, evidence-based summary for healthcare providers. Features include current Canadian recommendations, red flags to consider regarding the offer of NIPT, what the results mean, and the benefits and limitations of the test.

Prenatal Screening is available to all pregnant women in Canada. Different methods are used for prenatal screening, depending on the purpose and gestation. Here is a comprehensive guide to understanding prenatal screening [PDF], (https://www.geneticseducation.ca/uploads/patientresources/guide_to_prenatal_screening.pdf) an excellent patient resource (GECKO, n.d.-c).

With prenatal screening and detailed second-trimester ultrasound, the chance to have a baby with some specific genetic conditions or developmental differences can be more precisely determined. Prenatal screening is about risk assessment [PDF]. (https://www.geneticseducation.ca/uploads/patientresources/guide_to_prenatal_screening.pdf) (GECKO, n.d.-c).

Newborn screening tests (NBS) are done shortly after birth on a small blood sample (blood spot), taken by pricking the baby's heel. A nurse places a few drops of blood onto a special filter paper attached to a blood spot card (Perinatal Services BC, 2024). A NBS tests for treatable disorders that manifest their symptoms during childhood and are not otherwise easily identifiable at birth. This allows for early diagnosis and treatment. Unlike other types of genetic testing, a parent will usually only receive the result if it is positive. If the test result is positive, *additional testing is needed* to determine whether the baby has a genetic disorder. ISONG also has a position statement on newborn screening and the nurses' role [PDF] (https://www.isong.org/resources/Documents/Newborn%20ScreeningThe%20Role%20of%20the%20Nurse%20Updated%20Nov%202020.pdf). (MedlinePlus, 2023).

In Canada, each province is responsible for how it distributes health care funding and programming. Genetic services, including NBS, differ from province to province. The number of conditions screened for ranges from 14-36 (Groulx-Boivin et al., 2024). This creates a lack of equity in healthcare treatment across the country. Ongoing advocacy exists to establish a national NBS program (Canadian MPS Society, 2022).

Cascade testing tests family members of an individual with a pathogenic/likely pathogenic variants, usually who is affected by the condition. This process identifies other family members at risk of the hereditary condition (NCI, n.d).

Examples of genetic diagnostic tests

Molecular gene tests: These tests determine the order of DNA building blocks (nucleotides) in an individual's genetic code, a process called DNA sequencing. Molecular tests can also analyze RNA. The purpose of these tests is to identify pathogenic genetic variants. Molecular tests include polymerase chain reaction (PCR), fluorescent in situ hybridization (FISH) and next-generation sequencing (NGS) (MedlinePlus, n.d.-b).

Targeted single variant testing

Single variant tests look for a specific variant in one gene. The selected variant is known to cause a disorder

(for example, the particular variant in the *HBB* gene (https://medlineplus.gov/genetics/gene/hbb/) that causes sickle cell disease (https://medlineplus.gov/genetics/condition/sickle-cell-disease/)). This type of test is often used to test family members of someone known to have a particular variant to determine whether they have a familial condition (https://medlineplus.gov/genetics/understanding/inheritance/runsinfamily/) (MedlinePlus, n.d.-b).

Single gene testing

Single gene tests –Single gene tests look for any genetic changes in one gene. These tests are typically used to confirm (or rule out) a specific diagnosis, mainly when many variants in the gene can cause the suspected condition (CDC, 2024).

Genetic panel testing

Multigene panels – Panel tests look for variants in more than one gene. This type of test is often used to pinpoint a diagnosis when a person has symptoms that may fit a wide array of conditions or when the suspected condition can be caused by variants in many genes. (For example, there are hundreds of genetic causes of epilepsy) MedlinePlus, n.d.-b).

Large-scale genomic testing

Two methods, whole exome sequencing and whole genome sequencing, are increasingly used in healthcare and research to identify genetic variations; both methods rely on new technologies that allow rapid sequencing of large amounts of DNA. These approaches are **next-generation sequencing** (or next-gen sequencing) (CDC, 2024).

- **Whole exome sequencing** looks at *all the genes* in the DNA (whole exome) or those related to medical conditions (clinical exome). (MedlinePlus, n.d.-b; CDC, 2024).
- **Whole genome sequencing** is the most significant genetic test and looks at *all of a person's DNA, not just the genes*. (MedlinePlus, n.d.-b; CDC, 2024).

The original sequencing technology, called **Sanger sequencing** (named after the scientist who developed it, Frederick Sanger), was a breakthrough that helped scientists determine the human genetic code, but it was time-consuming and expensive. The Sanger method has been automated to make it faster and is still used in laboratories today to sequence short pieces of DNA, but it would take years to sequence a person's genome. Next-generation sequencing has sped up the process (taking only days to weeks to sequence a human genome) while reducing costs (Medline Plus, n.d.c).

With next-generation sequencing, it is now feasible to sequence large amounts of DNA, for instance, all of an individual's exons, the DNA that provides instructions for making proteins, which are thought to make up 1 percent of a person's genome. Together, all the exons in a genome are known as the **exome.** In whole exome sequencing, variations in the *protein-coding region* of any gene are identified, rather than in only a select few genes. Because most known variants that cause disease occur in exons, whole exome sequencing is considered an efficient method to identify possible disease-causing variants (Medline Plus, n.d.c).

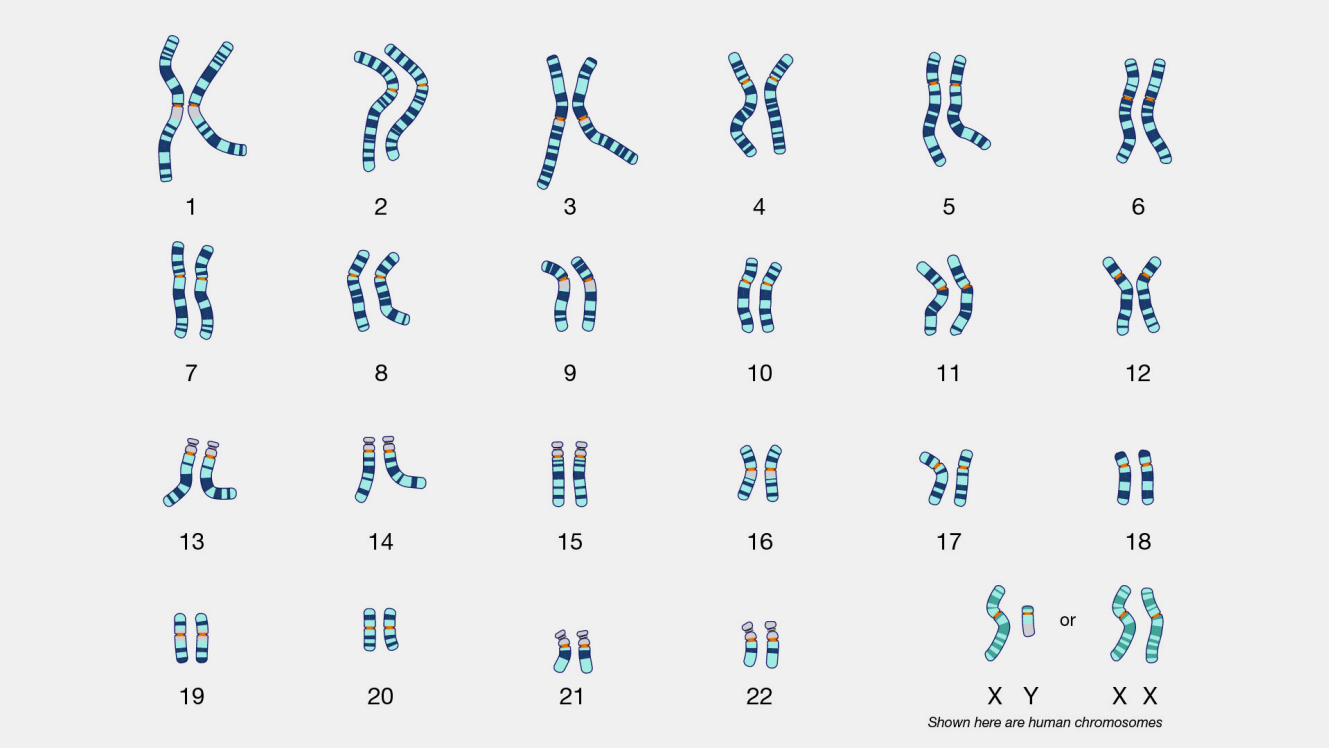
However, researchers have found that DNA variations outside the exons can affect gene activity and protein production and lead to genetic disorders–variations that whole exome sequencing would miss. Whole genome sequencing determines the order of all the nucleotides in an individual's DNA and can determine variations in any part of the genome (Medline Plus, n.d.c).

Whole exome sequencing or whole genome sequencing are tests that analyze the bulk of an individual's DNA to find genetic variations. Whole exome or whole genome sequencing (https://medlineplus.gov/genetics/understanding/testing/sequencing/) is typically used when a single gene or panel testing has not provided a diagnosis or when the suspected condition or genetic cause is unclear. Whole exome or whole genome sequencing is often more cost- and time-effective than performing multiple single gene or panel tests (MedlinePlus, n.d.-b).

Chromosomal tests: These tests analyze whole chromosomes or long lengths of DNA to identify large-scale changes, such as an extra or missing copy of a chromosome (trisomy or monosomy, respectively) or abnormalities of large segments of chromosomes, that underlie certain genetic conditions(MedlinePlus, n.d.-b).

A chromosomal microarray is a newer technology that might be recommended for a child with autism spectrum disorder. A karyotype is a high-level genomic test that analyses the number and structure of an individual's chromosomes (GECKO, n.d.-a).

More information on chromosomal microarrays vs karyotyping is available here [PDF] (https://pathwest.health.wa.gov.au/~/media/PathWest/Documents/Our-Services/Clinical-Services/Diagnostic-Genomics/CMA-and-Karyotype-Education-PPT.pdf). Additionally, see GECKO *on the Run:* (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/chromosomal-microarray/gecko-on-the-run-7) Chromosomal microarray – a 2-page, evidence-based summary for healthcare providers. Features a bottom line, red flags to consider microarray testing and genetic referral, what the results mean, and resources.



Source: Karyotype from Talking Glossary of Genomic and Genetic Terms Courtesy: National Human Genome Research Institute, PDM with attribution

Concept in Action

Watch Chromosomal Microarray Testing (4 mins) from Alberta Health Services on YouTube (https://youtu.be/ZrDANI0KSNU) to learn about chromosomal microarray testing.

Other tests

A full description of each of these tests is beyond the scope of this course. However, nurses may encounter these in research papers' methods sections. Therefore, it is beneficial to have a basic overview.

Gene expression tests

Genes are expressed, or turned on, at different levels in different types of cells. Gene expression tests compare these levels between normal and diseased cells because knowing the difference can provide important

information for treating the disease. For example, these tests can guide chemotherapy treatment for breast cancer (MedlinePlus, n.d.-b).

Biochemical tests

These tests look at levels or activity of proteins or enzymes produced by genes. Any abnormalities can signify underlying genetic disorders (MedlinePlus, n.d.-b). Metabolomics is a form of biochemical testing where levels of metabolites are measured. Samples such as urine, serum, and plasma can be tested for metabolites. Metabolomics is an emerging area of genetic research. Other forms of biochemical testing include protein assays such as colorimetric assays, immunoassays such as enzyme-linked immuno-absorbent assay (ELISA), mass spectrometry or gel electrophoresis (e.g. Western Blotting).

Epigenetic biomarkers

Other tests used in a clinical context include those looking for epigenetic markers. This is a rapidly evolving area of medical genetics research. Check out Epi-Sign (https://sadikoviclab.lhsc.on.ca/episign_info.html), used to obtain definitive diagnoses when other methods have returned uncertain results. This test examines DNA methylation patterns (biomarkers) associated with specific genetic disorders.

What is circulating tumour DNA, and how is it used to diagnose and manage cancer?

Circulating tumour DNA (ctDNA) is found in the bloodstream and refers to DNA from cancerous cells and tumours. Most DNA is inside a cell's nucleus. As a tumour grows, cells die and are replaced by new ones. The dead cells get broken down, and their contents, including DNA, are released into the bloodstream. ctDNA are small pieces of DNA, usually comprising fewer than 200 building blocks (nucleotides) in length.

The quantity of ctDNA varies among individuals and depends on the type of tumour, its location, and the cancer stage of cancerous tumours.

Detection of ctDNA can be helpful in the following cases:

- Detecting and diagnosing a tumour. Because tumour DNA has acquired multiple genetic variants, leading to tumour development, ctDNA is not an exact match to the individual's DNA. Finding DNA with genetic differences aids in tumour detection. Diagnosing the type of tumour using ctDNA can reduce the need to get a tumour tissue sample (tumour biopsy), which can be challenging when a tumour is difficult to access, such as a tumour in the brain or lung.
- Guiding tumour-specific treatment. Analyzing the genome of tumour cells using ctDNA can help doctors determine which treatment will be most effective. However, approval from the U.S. Food and

Drug Administration for ctDNA testing to personalize cancer treatment is limited.

- Monitoring treatment. A decrease in the quantity of ctDNA suggests the tumour is shrinking, and treatment is successful.
- Monitoring periods with no symptoms (remission of cancer). A lack of ctDNA in the bloodstream indicates that the cancer has not returned.

Clinical versus direct-to-consumer genetic tests

Clinical genetic tests are different from **direct-to-consumer (DTC) genetic tests**. A healthcare provider orders clinical genetic tests for a specific medical reason—an individual cannot order this type of testing. In contrast, anyone can buy DTC tests online (CDC, 2024). Other names for direct-to-consumer genetic testing include DTC genetic testing, direct-access genetic testing, at-home genetic testing, and home DNA testing. Ancestry testing (genealogy testing) is also considered a form of direct-to-consumer genetic testing (MedlinePlus, n.d.-d).

Many companies currently offer direct-to-consumer genetic tests for a variety of purposes. The most popular tests use a limited set of genetic variations to make predictions about certain aspects of health, provide information about common traits, and offer clues about a person's ancestry. The number of companies providing direct-to-consumer genetic testing and the range of health information these tests provide is growing. Because there is currently little regulation of direct-to-consumer genetic testing services, assessing the quality of available services before pursuing any testing (MedlinePlus, n.d.-d).

DTC test results can be used to decide lifestyle choices or identify issues to discuss with a healthcare provider. However, DTC tests cannot determine for sure whether or not the individual will get a disease. Nor should these tests be used alone to make decisions about treatment or medical care or in place of clinical genetic testing. However, patients present to medical professionals with reports generated from DTC testing. Therefore, healthcare providers must be aware that these tests exist and may be sought out by individuals who can pay for them (MedlinePlus, n.d.-d).

For more information, see GECKO *on the run* (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/direct-to-consumer-testing/gecko-on-the-run-9)*: (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/direct-to-consumer-testing/gecko-on-the-run-9)* Direct-to-consumer genomic testing – a 3-page, evidence-based summary for healthcare providers. Features include result interpretation, benefits and limitations of testing, and resources (GECKO, n.d.-d). The National Human Genome Research Institute also has an excellent resource on DTC testing for consumers (https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources/Healthcare-Provider-Direct-to-Consumer-Genetic-Testing-FAQ).

ISONG has a position statement on DTC genetic testing [PDF] (https://www.isong.org/resources/Documents/PS_Direct%20to%20Consumer%20GeneticGenomic%20Testing_September%202022.pdf). It concerns issues of informed consent, misinterpretation of test results, psychosocial concerns, confidentiality,

privacy, and integrity of specimens. The Canadian Medical Association also has a position statement on DTC genetic testing [PDF], (https://www.cma.ca/sites/default/files/2018-11/cma-policy-direct-to-consumer-genetic-testing-pd17-05-e.pdf) which considers the role of government and systems infrastructure in regulating DTC testing.

The Office of the Privacy Commissioner of Canada provides good consumer resources on privacy and DTC testing (https://www.priv.gc.ca/en/privacy-topics/health-genetic-and-other-body-information/02_05_d_69_gen/).

Attribution & References

Except where otherwise noted, this section is adapted from

- How are genetic screening tests different from genetic diagnostic tests? In *Help Me Understand Genetics* by MedlinePlus, Public Domain
- How is genetic testing done? In *Help Me Understand Genetics* by MedlinePlus, Public Domain
- What is circulating tumour DNA, and how is it used to diagnose and manage cancer? In *Help Me Understand Genetics* by MedlinePlus, National Library of Medicine, Public Domain with attribution
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8.4 INTERPRETING GENETIC TEST RESULTS

Genomic testing is becoming more affordable and accessible as it becomes more widely available and utilized in primary care and other non-specialized healthcare settings. However, this shift risks misinterpretation, as genomic reports are often complex, and healthcare providers may need more expertise or resources (GECKO, n.d). Misinterpretation is relatively common and can lead to unnecessary follow-up testing, inappropriate changes to clinical management, or false reassurance (GECKO, n.d.).

Variant Classification

Previously, pathogenic changes in the genome were called mutations (GECKO, n.d). More than 1% of the general population carries benign changes, which are referred to as *polymorphisms* (GECKO, n.d). Laboratories vary in how and what is reported. However, most accredited/licensed laboratories in Canada follow the American College of Medical Genetics and Genomics (ACMG) guidelines [PDF] (https://www.acmg.net/docs/standards_guidelines_for_the_interpretation_of_sequence_variants.pdf) (Richards et al., 2015). This is a five-tier system of classification of genomic variants. The ACMG classification framework organizes each of the criteria by the type of evidence (e.g. population data, functional data) as well as the strength of that evidence (e.g. very strong, strong, moderate, supporting) (Richards et al., 2015).

The ACMG classifications are recommended for describing pathogenicity in patients with suspected hereditary disorders, primarily Mendelian. This classification system is not meant to apply to somatic variants, pharmacogenomic variants, or complex disorders (Richards et al., 2015).

The five classifications of gene variants are:

- **Pathogenic**: The variant is responsible for causing disease. Ample scientific research supports an association between the disease and the gene variant. These variants are often referred to as mutations.
- **Likely pathogenic**: The variant is probably responsible for causing disease, but there is not enough scientific research to be certain.
- **Variant of uncertain significance (VUS or VOUS)**: The variant cannot be confirmed to play a role in disease development. There may be insufficient scientific research to confirm or refute a disease association or conflicting research.
- **Likely benign**: The variant is probably not responsible for causing disease, but there is not enough scientific research to be certain.
- **Benign**: The variant is not responsible for causing disease. There is ample scientific research to disprove

an association between the disease and the gene variant.

Source: Genomic Test Results GECKO on the run by Genetics Education Canada: Knowledge Organization (GECKO), reprinted with permission. See the GECKO website for text-based version (https://geneticseducation.ca/resources-for-clinicians/genomic-technologies/genomic-test-results/gecko-on-the-run).

Evaluation needs to be done for each variant. Just because a gene is associated with a disease does not mean that all variants in that gene are pathogenic. Additionally, a variant must be evaluated for all diseases with which it is thought to be associated. A pathogenic variant for one disease is not necessarily pathogenic for a different disease. It is important to re-evaluate variants periodically; the classification of a variant can change over time as more information about the effects of variants becomes known through additional scientific research.

A positive test result means that the laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the test's purpose, this result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic variant, identify an increased risk of developing a disease (such as cancer), or suggest further testing. Because family members have some genetic material in common, a positive test result may also have implications for certain blood relatives of the person undergoing testing. It is important to note that a positive result of a predictive or presymptomatic genetic test usually cannot establish the exact risk of developing a disorder. Also, healthcare providers typically cannot use a positive test result to predict the course or severity (https://medlineplus.gov/genetics/understanding/consult/prognosis/) of a condition. Rarely test results can be false positive, which occurs when results indicate an increased risk for a genetic condition when the person is unaffected.

A negative test result means that the laboratory did not find a change that affects health or development in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic variant, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration because many tests cannot detect all genetic changes that can cause a particular disorder. Further testing or re-testing at a later date may be required to confirm a negative result. Rarely, test results can be false negative, which occurs when the results indicate a decreased risk or a genetic condition when the person is affected.

In some cases, a test result might not give any useful information. This type of result is called uninformative, indeterminate, inconclusive, or ambiguous. Uninformative test results sometimes occur because everyone has common, natural variations in their DNA, called polymorphisms, that do not affect health. If a genetic test finds a change in DNA that has not been confirmed to play a role in the development of disease, known as a variant of uncertain significance (VUS or VOUS), it can be difficult to tell whether it is a natural polymorphism or a disease-causing variant. For these variants, there may not be enough scientific

research to confirm or refute a disease association or the research may be conflicting. An uninformative result cannot confirm or rule out a specific diagnosis, and it cannot indicate whether a person has an increased risk of developing a disorder. In some cases, testing other affected and unaffected family members can help clarify this type of result.

While many more genetic variants can be identified with whole exome and whole genome sequencing than with select gene sequencing, the significance of much of this information is unknown. Because not all genetic changes affect health, it is difficult to know whether identified variants are involved in the condition of interest. **Secondary findings** are a part of the analysis performed but are not related to the reason the test was performed in the first place (National Society of Genetic Counsellors, 2023). **Incidental findings** are also unrelated to the initial reason for testing but are detected unexpectedly (National Society of Genetic Counsellors, 2023).

Concept in Action

Watch this very brief video – Let's talk about incidental findings (3 mins) on Vimeo (https://vimeo.com/451880672)

In 2013, the American College of Medical Genetics and Genomics (ACMG) recommended that all labs performing whole exome and whole genome sequencing tests report particular secondary findings, in addition to any variants that are found related to the primary purpose of the testing. In the 2025 updated recommendations, ACMG proposed a list of 84 genes that are associated with a variety of conditions, from cancer to heart disease. The 84 genes for which secondary findings are reported were chosen because they are associated with conditions that have a definable set of clinical features, the possibility of early diagnosis, a reliable clinical genetic test, and effective intervention or treatment. The goal of reporting these secondary findings to an individual is to provide medical benefit by preventing or better managing health conditions. The variants that are reported are known to cause disease. Variants of unknown significance, whose involvement in disease at the current time is unclear, are not reported.

The information provided by secondary findings can be very important because it may help prevent a disease from occurring or guide the management of signs and symptoms if the disease develops or is already present. However, as with any type of medical diagnosis, the news of an unexpected potential health problem may lead to additional health costs and stress for individuals and their families. On the basis of secondary findings, additional testing to confirm results, ongoing screening tests, or preventive care may be advised. Individuals receiving whole exome or whole genome sequencing can choose to "opt out" of analysis of the 84 secondary finding genes and not receive variant results. As whole exome and whole genome sequencing become more common, it is important for individuals to understand what type of information they may learn and how it can impact their medical care.

Nursing Implications

Nurses play a pivotal role in supporting patients undergoing genetic testing by providing comprehensive patient education, facilitating informed consent, and fostering shared decision-making. They ensure patients understand the purpose, potential outcomes, and implications of genetic tests, addressing emotional and ethical considerations. Nurses guide patients in evaluating options and preparing for the results, promoting autonomy and informed choices. They collaborate closely with genetic counselors and geneticists, referring patients for specialized consultations when necessary to enhance care quality and optimize health outcomes. This interdisciplinary approach ensures patients receive holistic, informed, and compassionate care throughout the genetic testing process. Nurses need to be aware of the scope, responsibilities, and accountabilities of other members of the genomics healthcare team so they can appropriately refer patients (CDC, 2024).

The Role of Genetic Counselors

The National Society of Genetic Counselors (National Society of Genetic Counsellors, 2023) recommend individuals have counseling before obtaining genetic testing to plan how results will be returned, including secondary or incidental findings. Genetic counseling before genetic testing can help decide who is the right person in a family to get a genetic test and can help ensure the right tests are ordered. Genetic counseling after genetic testing can help patient's understand their results. Large-scale genetic tests can have findings unrelated to why the test was ordered in the first place.

Attribution & References

Except where otherwise noted, content on this page is adapted from Do all gene variants affect health and development? , What do the results of genetic tests mean? , What are whole exome sequencing and whole genome sequencing? and What are secondary findings from genetic testing? In *Help Me Understand Genetics* by MedlinePlus, Public Domain

- Nursing implications section written by Andrea Gretchev, CC BY-NC 4.0

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8.5 UNIT SUMMARY AND REVIEW

Key Takeaways

Genetic testing analyzes DNA, genes, chromosomes, or proteins to identify changes associated with health conditions. It serves various purposes, including predicting disease risk, identifying carriers of genetic conditions, diagnosing disorders, guiding treatment decisions, and informing research. Examples include newborn screening, prenatal testing, carrier screening, pharmacogenomic testing, and diagnostic tests. The benefits include reducing uncertainty about health risks, guiding preventive measures, and aiding treatment planning. However, testing has limitations, such as emotional, financial, and social implications, potential discrimination, and gaps in actionable treatments for identified disorders. Nurses play a critical role in patient education, informed decision-making, and coordination with genetic counsellors.

Genomic testing is becoming more accessible and integrated into primary care, yet its complexity raises challenges, particularly around interpreting results. Canadian laboratories typically classify genomic variants into five categories—pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign—using guidelines like those from the American College of Medical Genetics and Genomics (ACMG). Misinterpreting results can lead to unnecessary follow-up, improper clinical management, or false reassurance. Secondary findings, unrelated to the primary reason for testing but may provide actionable health insights, are increasingly reported in whole exome and genome sequencing. However, they can also pose ethical and emotional challenges. Pre- and post-test counselling is essential to help individuals understand the implications of these findings and plan for their medical care.

Resource

1. Lee, K., Abul-Husn, N. S., Amendola, L. M., Brothers, K. B., Chung, W. K., Gollob, M. H., Gordon, A. S., Harrison, S. M., Hershberger, R. E., Li, M., Ondrasik, D., Richards, C. S., Stergachis, A., Stewart, D.

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Additional Optional Readings

1. Gasperskaja, E., & Kučinskas, V. (2017). The most common technologies and tools for functional genome analysis. *Acta Medica Lituanica, 24*(1), 1–11. https://doi.org/10.6001/actamedica.v24i1.3457
2. Smith L. P. (2019). The spectrum of genetic testing. Seminars in Oncology Nursing, 35(1), 11–21. https://doi.org/10.1016/j.soncn.2018.12.008

Attribution & References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

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