UNIT 12 - GENOMICS APPLICATIONS

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.

Unit 12 Contents

Attribution

12.1 UNIT OVERVIEW

Learning Objectives

- Identify the direct and indirect health consequences of environmental phenomena such as climate change, pollution, and natural disasters.
- Briefly explore the relevance of genomics to oncology.
- Distinguish between types of genomic variants in cancer.
- Examine various way genomics aids diagnosis and treatment in different medical specialties

Outline

Topics covered in this chapter include:

- Global health and genomics
- Cancer genomics
- Genomics applications by specialty

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.

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;
- based on an awareness of the care pathways relevant to your role that incorporate genomics services and information; and
- taking appropriate and timely action to seek assistance from and refer individuals to genomics specialists, other specialists and peer support resources.

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; 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:

- recognizing areas where professional development related to genomics would be beneficial;

- maintaining awareness of clinical developments in genomics that are likely to be of most relevance to your area of practice, seeking further information on a case-by-case basis; and
- 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.

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

- being responsive to changing needs through the life-stages and during periods of uncertainty; and
- demonstrating awareness about how a genomic test result can have implications for family members and might impact on family dynamics.

Key terminology

Circulating tumour DNA (ctDNA)

As cancer cells grow very fast and die, they release some of their DNA into the bloodstream. We now have tests that are sensitive enough to detect and sequence these pieces of ctDNA in the bloodstream separately from the normal DNA of the patient – this is called a "liquid biopsy" (NHGRI, n.d.a).

BRCA1/2

BRCA1 and BRCA2 are the first two genes found to be associated with inherited forms of breast cancer and ovarian cancer. People with variants in either BRCA1 or BRCA2 have a much higher risk for developing breast, ovarian or other types of cancer than those without variants in the genes. Both BRCA1 and BRCA2 normally act as tumor suppressors, meaning they help to regulate cell division. Most people have two active copies of these genes. When one of the two copies becomes inactive due to an inherited variant, a person's cells are left with only one copy. If this remaining copy also becomes inactivated, then uncontrolled cell growth results, which leads to breast, ovarian or other types of cancer.

Attribution & References

Except where otherwise noted, this page is adapted from:

- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.

References

American Nurses Association (ANA). (2023). *Essentials of genomic nursing: Competencies and outcome indicators* (3rd ed.). https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/

National Human Genome Research Institute (NHGRI). (n.d.a). *Cancer genomics*. https://www.genome.gov/dna-day/15-ways/cancer-genomics

National Human Genome Research Institute (NHGRI). (n.d.b). *Talking glossary of genetic and genomic terms*. https://www.genome.gov/genetics-glossary

12.2 GENOMICS AND GLOBAL HEALTH

How the Environment and Genetics Shape Health Outcomes

In Unit Three, we examined the interplay between the environment and genetics in shaping health outcomes. The evidence for climate change is undeniable, as demonstrated by the increasing frequency and intensity of forest fires, floods, warming oceans, hurricanes and weather terms that have become a part of our vernacular like heat domes, atmospheric rivers, and cyclone bombs. These events have profound direct effects on environmental health and biodiversity which, in turn, impact human physical, mental, and social health. Additionally, indirect effects emerge through exposure to environmental toxins such as pollution and forest fire smoke, disruptions to the food chain, and the rising costs of essential goods. Global pandemics, often exacerbated by environmental degradation and changes in human-animal interactions, further illustrate the far-reaching health consequences of a disrupted ecosystem. Our ecosystem is an interconnected system, and when one link is disrupted, the consequences ripple broadly across all aspects of life.

Watch GenARCC | Will Canadian species be able to adapt to climate change? (5 mins) on YouTube (https://youtu.be/pKGzvffK6uA)

Read

The following article examines the role of genetic variation and environmental exposures, such as toxicants, pollution, and viruses, in disease pathogenesis. Applied examples include Chron's disease and cystic fibrosis. Genomics offers tremendous potential for global public health but there are also significant challenges to overcome.

Virolainen, S. J., VonHandorf, A., Viel, K. C. M. F., Weirauch, M. T., & Kottyan, L. C. (2023). Gene-environment interactions and their impact on human health. *Genes and immunity*, *24*(1), 1–11. https://doi.org/10.1038/s41435-022-00192-6

OPEN ACCESS ONLINE

In 2022, the World Health Organization (WHO) Science Council produced a report (https://www.who.int/publications/i/item/9789240052857) containing 15 recommendations for WHO to promote the current and future use of genomic technologies for global health.

Some examples of ways in which genomics is used for global health include:

- Genomic surveillance for pathogens with pandemic and epidemic potential (https://www.who.int/initiatives/genomic-surveillance-strategy)
- Using genomic surveillance to track MRSA "superbugs" (https://www.yourgenome.org/theme/using-genomic-surveillance-to-track-mrsa-superbugs/)
- Using phylogenetics (the study of evolutionary relationships between organisms) to track disease outbreaks (https://www.yourgenome.org/theme/using-phylogenetics-to-track-disease-outbreaks/)
- Examining genetic and environmental factors influencing health disparities (https://globalgenomics.med.upenn.edu/)
- Using genomics to understand malaria (https://www.yourgenome.org/theme/using-genomics-to-understand-malaria/)

Concept in Action

Watch how genomic surveillance can be used to track diseases with pandemic potential in COVID-19 Genomic Surveillance (5 mins) on YouTube (https://youtu.be/hiX7jvdE8KI)

To effect change, global health must be addressed at the policy level. Genomics-informed global health research can provide evidence for policy development to address the impacts of climate change on the health of populations through monitoring and mitigating environmental health risks. Genomic surveillance can be utilized to track pathogens as part of a pandemic preparedness public health strategy. Genomic sciences can help to identify genetic and environmental factors that contribute to health disparities in order to promote greater health equity. Additionally, developing policies that recognize the interconnectedness of the environment and human health can help reduce environmental degradation and associated health risks.

Attribution & References

12.3 CANCER GENOMICS

Proto-oncogenes

Recall from chapter 2.4 that control of cell division involves many different genes. Some of these genes act as signaling molecules to activate normal progression through the cell cycle. Think of oncogenes as the "accelerators" of cell growth and proliferation. One of the pre-requisites for cancer occurs when one or more of these activators of cell division become altered. Proto-oncogenes are normal genes that, when altered, become oncogenes and contribute to cancer as they code for positive cell-cycle regulators.

Tumour Suppressor Genes

Tumor suppressor genes act like the "brakes" of the cell cycle, preventing uncontrolled growth and promoting repair. More than 30 genes, including *BRCA1* and *p53*, are classified as tumor suppressors. These genes repair DNA, induce apoptosis, and prevent abnormal cell division. Loss-of-function variants in these genes contribute to cancer progression, and both alleles must be varied (loss of heterozygosity) for abnormal growth to proceed.

Why is genomics important in cancer care?

Cancer is a disease of the genome. It occurs when variants in the genome result in uncontrolled cell growth and division. These genomic variants can be inherited from a parent or acquired at some point during a person's lifetime. Most cancers are caused by acquired genomic variants. In around 5%-10% of cases, the individual has inherited a variant that greatly increases their chances of developing cancer.

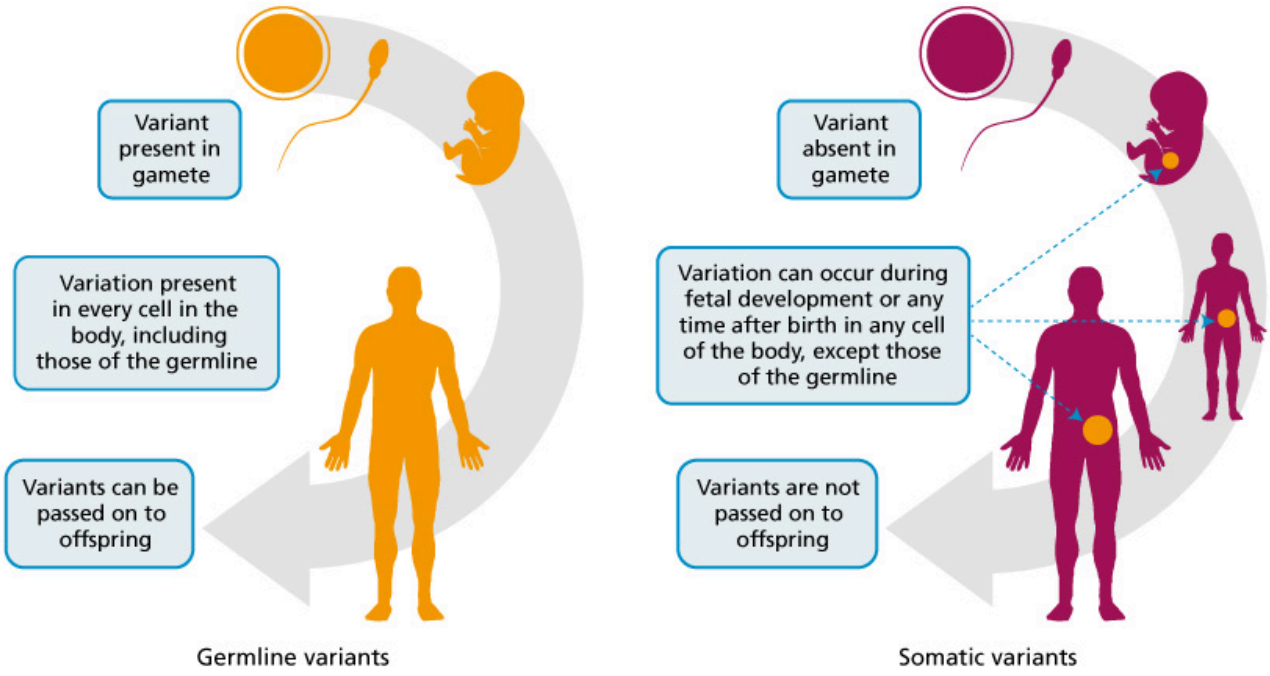

Figure 12.1. Inherited (germline) genomics variants vs acquired (somatic) variants. **Germline variants:** Variant present in gamete. Variation present in every cell in the body, including those of the germline. Variants can be passed on to offspring. **Somatic variants:** Variant is absent in gamete. Variation can occur during fetal development or any time after birth in any cell of the body, except those of the germline. Variants are not passed on to offspring. **Source:** Genomics Education Programme, CC BY-NC 4.0.

Cancer care has rapidly evolved, particularly over the last 15-20 years. View genomics milestones in oncology (http://media.mycrowdwisdom.com.s3.amazonaws.com/ons/_ACTIVE/MILESTONES/story.html) using this Genomic Milestones interactive site.

Two kinds of cancer variants

Inherited variants

Inherited genomic variants are also called germline variants. For an individual with a cancer predisposing germline variant (i.e. known to be pathogenic or likely pathogenic) each cell in their body already has an altered copy (see ch. 8.4 – Interpreting Genetic Tests) . This significantly increases their lifetime risk of cancer.

A patient with this type of variant may be offered additional screening or prophylactic surgery. For example, patients with particular *BRCA1* and *BRCA2* gene variants that are known to be pathogenic or likely pathogenic may opt for enhanced breast screening protocols, preventative medications, and reproductive health planning and counselling. An additional option is to have a preventative mastectomy or oophorectomy.

It is also important to consider the implications for the patient's family, as appropriate testing (cascade testing) can identify other at-risk relatives who may be able to take measures to reduce their chance of developing cancer. Therefore, not only do nurses need to consider the autonomy of their patient, but their relational autonomy, including their networks and relationships that factor into their decision-making.

Acquired variants

Acquired genomic variants are called somatic variants, and these variants are present only in cancer cells. These variants are not inherited and cannot be passed on to any children.

Somatic variants can be the result of exposure to environmental factors, such as ultraviolet light, smoking, radiation and alcohol, or they can be entirely random. Each time a cell divides, errors might be introduced. While there are many mechanisms within the cell to correct these errors, occasionally they are missed.

Is cancer hereditary?

The term hereditary cancer is a bit misleading. It is important to note that not all cancers are hereditary and for those that are, cancer itself cannot be inherited. Specifically, somatic variants in tumour cells are not passed down to offspring. However, an inherited germline genetic variant ***increases the risk of developing certain types of cancer*** because at birth they have inherited one altered "copy" of the cancer causing gene. Inheriting a variant does not guarantee that person will develop cancer. However, their risk is increased over those without the specific variant for particular types of cancer.

For example, if a parent passes a *BRCA1* or *BRCA2* gene variant to their child, the child will have a much higher risk of developing breast and several other cancers. That's why cancer sometimes appears to run in families.

Watch Genomics in Medical Specialties – Oncology: Cancer Treatment (3 mins) on YouTube (https://youtu.be/Putm4DHuj84)

Blood Tests to Detect Cancer

Did you know that we are increasingly able to detect cancers by testing just a blood sample? Or that we are moving toward treating cancers not by where they are found in the body, but by how their genomes have changed? Cancer is caused by changes in an individual's genome, but advances in DNA sequencing technology are leading to a new understanding of cancer and new ways for diagnosing and treating many types of cancer.

Cancer is a group of genetic diseases that result from changes in the genome of cells in the body, leading them to grow uncontrollably. These changes involve DNA variants in the genome. Our cells are constantly finding and fixing variants that occur in our genome as the cells divide over and over again. But on rare occasions, some variants slip through our cells' repair machinery, and those variants can lead to cancer. The Human Genome Project has allowed us to establish what "normal" usually looks like for a human genome, so that we can now tell when changes in our genome have taken place that lead to cancer.

Large projects around the world, like The Cancer Genome Atlas (https://cancergenome.nih.gov/) in the United States and the Catalogue of Somatic Mutations (http://cancer.sanger.ac.uk/cosmic) (COSMIC) in the United Kingdom, have now determined the genome sequences of thousands of cancer samples of many cancer types. These projects have shown that some cancers have variants in the same group of genes, even though they may have started in completely different tissues. Many of the variants activate genes that normally promote cell growth or break genes that normally prevent cell growth. If we know more about the specific variants that led to someone's cancer, no matter what tissue it was located in, then we can look for more specific and effective treatments for their cancer.

Unfortunately, some cancers are harder to evaluate because looking at their genomes would require difficult and painful biopsies or operations where tiny parts of the cancer tissue are removed for study. This also makes it harder for clinicians to monitor how treatment is working for some cancers because repeated biopsies are just not possible. Recent breakthroughs now allow the detection of **circulating tumour DNA** (or ctDNA (https://www.labroots.com/videos/3156/liquid-biopsy-when-blood-reveals-cancer-s-story)) in the blood of patients instead of directly sampling the tumour. As cancer cells grow very fast and die, they release some of their DNA into the bloodstream. We now have tests that are sensitive enough to detect and sequence these pieces of ctDNA in the bloodstream separately from the normal DNA of the patient – this is called a "liquid biopsy."

Although liquid biopsies are not yet in widespread use for cancer detection, improvements are being made all the time that move us closer to the routine use of ctDNA tests (http://www.cnn.com/2018/01/19/health/cancer-blood-test-study/index.html). One of the current approved uses for ctDNA is to test progression of non-small cell lung cancer (http://www.phgfoundation.org/documents/developing-effective-ctdna-services-for-lung-cancer.pdf) by looking for specific variants in the *EGFR* gene over time. Liquid biopsies (http://www.phgfoundation.org/documents/developing-effective-ctdna-services-for-lung-cancer.pdf) can point to who will likely relapse after treatment, by detecting DNA with *EGFR* variants that is circulating in the blood, sometimes better and more quickly than the now-used standard imaging techniques. The CHARM study is ongoing in five Canadian provinces. Visit their website cfDNA in Hereditary and High-Risk Malignancies (CHARM) study (https://charmconsortium.ca/about/). This is an excellent example of research revolutionizing how hereditary cancer syndromes can be managed in practice. Their aim is to to develop a blood test to predict cancer development in carriers of cancer predisposition genes including *BRCA1, BRCA2, PALB2* (hereditary breast and ovarian cancer) *CDH1* (hereditary diffuse gastric cancer)

MLH1, MSH2, MSH6, PMS2, EPCAM (Lynch syndrome) *TP53* (Li-Fraumeni syndrome) using circulating tumour DNA. On an international level, the CASCADE (https://swisscascade.ch/en/home/) study aims to provide support and care coordination to families with pathogenic variants connected to breast and ovarian cancer and to Lynch syndrome.

Refining treatment

Some genomic variants within the cancer genome can be used to work out the most appropriate treatment for the patient. Some variants can make the person more, or less, likely to respond well to particular treatments.

For example, tumours with certain variants in the *EGFR* gene respond well to EGFR-inhibitor drugs, but those without such variants do not. So two people with the same diagnosis of breast cancer may have different treatments based on the genomic information from their tumour.

Novel treatments can also be identified by sequencing (https://www.genomicseducation.hee.nhs.uk/glossary/sequencing/) the tumour's genome.

Listen to specialist registrar Dr Alison Berner discuss the impact this is having on patients. **Watch The Realisation of Personalised Medicine (3 mins) on Vimeo (https://vimeo.com/336816796).**

By far, most cancers are not inherited, but there are a few examples of inherited cancers like Lynch syndrome (also known as hereditary non-polyposis colorectal cancer). This disorder is due to inherited variants in any of five different genes (https://ghr.nlm.nih.gov/condition/lynch-syndrome#genes), and leads to an increased risk of different types of cancers, most often in the colon. Breast cancer is another example; again most cases are not inherited, but men or women who have inherited variants in the *BRCA1* or *BRCA2* genes have a much higher chance for developing breast cancer than other people.

Table 12.1. High and moderate-penetrance genes in breast and gynecologic cancer Source: National Cancer Institute (NCI) (2024).

High penetrance breast and/or gynecologic cancer susceptibility genes	Moderate-penetrance genes associated with breast and/or gynecologic cancers
BRCA1 and *BRCA2*	Fanconi anemia genes
Lynch Syndrome	*CHEK2*
Li-Fraumeni Syndrome (LFS)	*ATM*
PTEN Hamartoma Tumor Syndromes (Including Cowden Syndrome)	*RAD51*
Hereditary Diffuse Gastric Cancer (HDGC)	*SMARCA4*
Peutz-Jeghers Syndrome (PJS)	–
PALB2	–
De Novo Pathogenic Variant Rate	–

As we learn more about the genomic changes predisposing a person to cancer, we have been able to make screening tests available to many more people. The specific DNA sequences of the *BRCA1* and *BRCA2* genes were even the subject of a legal case (https://en.wikipedia.org/wiki/Association_for_Molecular_Pathology_v._Myriad_Genetics,_Inc.)that went all the way to the United States Supreme Court, who ruled that the sequences of your genes could not be patented. Before this ruling, only one company could provide *BRCA1* or *BRCA2* testing in the United States, but now there are a number of companies who can help if you'd like to have genomic testing for hereditary causes of breast cancer.

Tom explains what genetic testing means to him and how he benefited from the information it provided.

Watch Tom's story: Genomic testing and treatment for Lynch syndrome (3 mins) on YouTube.

Appropriate Referrals

Oncology nurses are often a primary point of contact for oncology patients. Oncology nurses collect comprehensive health histories including family histories that may include findings indicative of possible hereditary cancer predisposition. The Oncology Nursing Society (ONS) has created this excellent handout *Why it is Important to know if Your Patient's Cancer is Hereditary,* (https://www.ons.org/clinical-tools/resources/when-refer-genetics-professional-quick-guide) which details the hereditary and red flag indicators

that the patient would benefit from further consultation for genetic testing (click the link then click "download .pdf). Oncology nurses should become familiar with the protocols in their jurisdiction about how to initiate referrals for further consultation or genetic testing when they find health assessment data suggestive of a possible hereditary cancer predisposition.

Oncology Resources

This unit provided a brief introduction to oncology genomics, as within this practice context genomics is extensively integrated. Nurses working in oncology need more than a foundational level of genomic literacy. There are ample professional development opportunities available for nurses wishing to learn more about this important area of genomics nursing.

Nursing organizations

- The Oncology Nursing Society (ONS) have a wealth of professional development resources for oncology nurse members, including a Genomics and Precision Oncology Learning Library (https://www.ons.org/genomics-and-precision-oncology-learning-library).
- The Canadian Association of Nurses in Oncology also has numerous resources for Canadian oncology nurses, including a Genomics Oncology Nursing Special Interest Group (https://www.cano-acio.ca/page/genomics).

Student membership is free for both of these organizations!

- Linkage (LInking Nursing Knowledge And GEnomics) has online learning modules (https://linkage.trubox.ca/learning-modules/module-4/), including one on cancer genomics.

Oncology Genomics

- The National Comprehensive Cancer Network (NCCN) provides an excellent clinical resource Guidelines for Treatment by Cancer Type (https://www.nccn.org/guidelines/category_1), and cancer Detection, Prevention, and Risk Reduction (https://www.nccn.org/guidelines/category_2).
- My Cancer Genome (https://www.mycancergenome.org/) offers genetically-informed cancer medicine resources including current information on variants, therapeutic implications, and clinical trials.
- The National Cancer Institute has a cancer genetics overview for healthcare professionals (https://www.cancer.gov/publications/pdq/information-summaries/genetics/overview-hp-pdq).

Attribution & References

References

National Cancer Institute (NCI). (2024, November 22). *Genetics of breast and gynecologic cancers (PDQ®) – Health professional version.* https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#_156

12.4 GENOMICS APPLICATIONS BY SPECIALTY

While numerous practice areas are still progressing toward widespread integration of genomics into routine medical practices, certain specialties have seen more substantial advancements, often due to greater research funding or the strategic prioritization of genomics implementation. While the previous chapter focused on oncology as a leading example where the integration of genomics is well-established and extensively applied, key resources and emerging practices in each of these other five practice areas are provided to highlight the growing prevalence of genomics: pediatrics, maternity/obstetrics, mental health, neurology, and cardiology. It should be noted that the relevance of genomics is not limited to these practice areas.

Pediatrics

Units three and four briefly introduced a number of genetic conditions that manifest in childhood, along with early adverse experiences and their influence on the epigenome.

Recent advances in genomics mean that increasing numbers of children and their families can benefit from genomic testing. Testing can provide new diagnoses, shape management decisions, guide treatment options and provide valuable information.

Many genomic conditions affect early development, leading to congenital structural malformations and/or neurodevelopmental delay. This means that individuals with genomic conditions will commonly present in childhood.

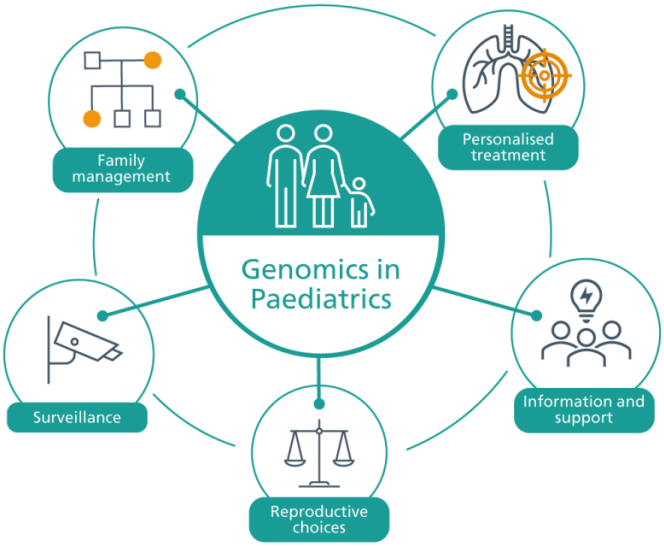

Figure 12.2. Examples of genomics in pediatric practice include family management, personalised treatment, information and support, reproductive choices and surveillance. **Source:** Genomics Education Programme, CC BY-NC 4.0

Identifying a diagnosis can help patients and their families in a wide variety of ways. Some examples are outlined below.

Information and support

Having a genomic diagnosis often allows the patient and their family – as well as other healthcare professionals – to learn more about their condition, understand the health implications in the short and long term, and access family support groups, which may be helpful from both an emotional and an educational perspective. Support groups often inform their members about developments in the field, including research and clinical trials.

Surveillance

Some pediatric genomic conditions are associated with specific health complications, such as an increased risk of developing early childhood tumours. For some of these complications, specific surveillance guidelines have been developed and published; this means that if the genomic condition is diagnosed early on, the child will have timely access to a condition-specific surveillance program that could improve their healthcare outcomes by identifying and enabling management of complications (which may include personalized treatments) at an early stage.

Personalized treatment

In some cases, a genomic diagnosis provides access to personalized treatment. Some examples of this are outlined below.

- The use of commonly-used drugs proven to be particularly effective in a specific genomic condition. For example, the anticonvulsant retigabine (ezogabine) has particular efficacy in treating epilepsy caused by loss-of-function variants in the *KCNQ2* gene.
- The avoidance of certain medications. For example, some babies (1 in 500) are born with a particular genetic variant that means that administering the antibiotic gentamicin will cause irreversible hearing loss; however, new technologies have enabled clinicians to test for this genetic variant with a single cheek swab, which has a 15-minute turnaround time for results and means that use of gentamicin can be avoided where necessary.
- The use of targeted therapies – many of which are in development – such as enzyme replacements, dietary restrictions or gene therapies. For example, patients with spinal muscular atrophy are now benefiting from treatment with nusinersen (widely marketed as Spinraza (https://www.spinraza.com/)), a drug that is delivered directly to the central nervous system to target an underlying cause of motor neuron degeneration.

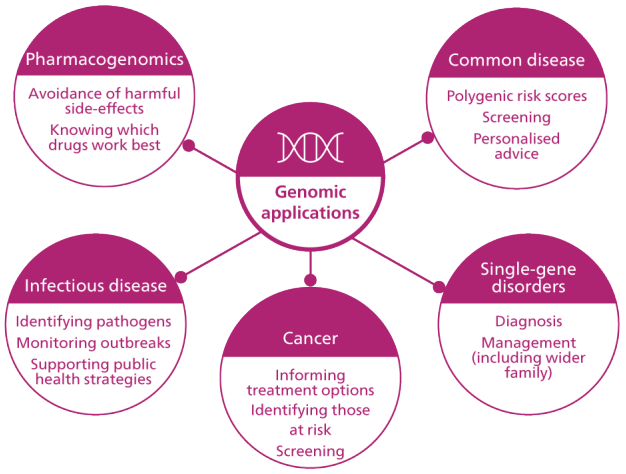

Figure 12.3. Genomic applications appears in a circle in the centre. Branching off from this is pharmacogenomics, common disease, single-gene disorders, cancer, and infectious disease. **Source:** Genomics Education Programme, CC BY-NC 4.0

Family management and reproductive choices

Because we share some of our DNA with people to whom we are genetically related, genomic conditions can have implications for our family members. This means that we must consider the inheritance pattern of any genomic diagnosis. It may be appropriate to offer parental testing, which helps to clarify any inheritance patterns and potential risks to immediate family members. For some conditions, it may be appropriate to offer cascade testing to the wider family.

Where there is a significant chance of future pregnancies being affected by the same genomic condition, some couples may wish to make complex, personal reproductive choices that may include a normal pregnancy (sometimes with additional scans or screening), use of donated sperm, egg and/or embryo, adoption, prenatal diagnosis or pre-implantation genetic diagnosis (PGD). Prenatal diagnosis is usually performed through chorionic villus sampling between 11 and 14 weeks of pregnancy. PGD is an IVF-based technique in which embryos are screened and only those without the familial genomic variant are transferred into the womb. In these scenarios, your role as a pediatrician would be to refer your patients to the appropriate specialist team – be it genetic counselling, fetal and women's health or clinical genetics.

Finally, children with a genomic condition may be anxious about and want to discuss the implications of their diagnosis for any future children they themselves may have. An understanding of the inheritance patterns of genomic conditions will help you, as a pediatrician, to have those conversations with affected children.

The number of ways in which genomics can be applied in pediatrics will only increase with time. Take a look at the diagram below to find out some of the ways in which genomics is already being used to improve pediatric patient outcomes.

Case Example: Bardet-Biedl Syndrome

- Antenatally, George was found to have an echogenic kidney (a kidney that appears bright in an ultrasound, indicating a possible condition). He was also born with an extra fifth digit (a condition known as polydactyly), and was consequently referred to the clinical genetics team.

- When George was reviewed by the clinical genetics team as a baby, results of microarray testing and a postnatal renal ultrasound scan were both normal.
- George was followed up by the clinical genetics team until the age of two. There were no further suspicions of a genetic disorder, so he was discharged back to pediatric care, where he was later managed for developing obesity and mild learning difficulties.
- Due to evolving genomic technologies, George was then recruited into a research study into early-onset obesity by his pediatrician.
- Two years later, the research study found two variants in George's *BBS5* gene, indicating a diagnosis of autosomal recessive Bardet-Biedl syndrome (BBS).
- As well as presenting a cause for George's polydactyly, obesity and learning difficulties, this new diagnosis had important implications for his management and prognosis. Sadly, most individuals with BBS become blind by their second or third decade of life.
- George was referred back to the clinical genetics team for further support and counselling about the condition, while his pediatrician made clinical referrals to the ophthalmology, audiology, endocrinology and renal teams for surveillance of his syndromic manifestations.

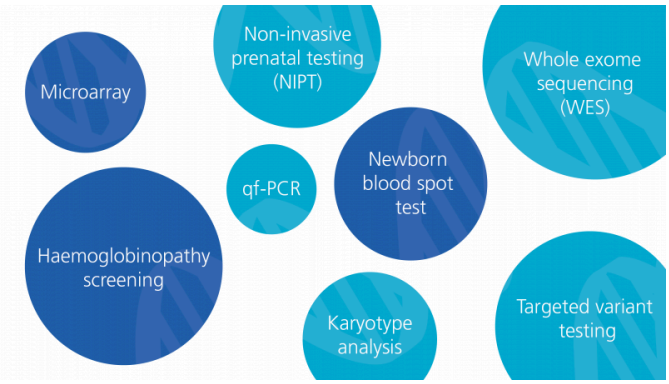

Figure 12.4. Genomics testing used in pregnancy and family planning. Various circles containing the names of genomics tests used in pregnancy and family planning including: microarray, non-invasive prenatal testing, hemoglobionopathy screening, newborn blood spot test, qf-PCR, whole exome sequencing, targeted variant testing, and karyotype analysis.
Source: Genomics Education Programme, CC BY-NC 4.0

Maternity

Genomics will continue to play more of a role in the diagnosis, management and treatment pathways for parents and their babies. Expectant parents need nurses who are knowledgeable, confident and competent so it's paramount to ensure your genetics and genomics knowledge and skills are up to date with the latest developments. This will allow them to make choices with conviction and courage. Information is easier than ever to access online and people are now more aware about genomics – they could even know something that the nurse does not. Be prepared for questions and know where you can find accurate answers.

There is some overlap between maternity and pediatric specialties, depending on when a genetic condition is suspected or diagnosed. Nurses may care for patients at any point in their family planning or pregnancy journey, depending on their context of practice. Pre-natal, antenatal, and postnatal screening was briefly covered in unit eight. This will not be revisited here except to mention that it is nurses that typically obtain

specimens for genetic screening in these contexts. To provide appropriate informed consent, nurses must know what the tests might reveal and the risks and benefits of testing.

Some types of tests are indeed ***genetic***, because they test for a condition by looking for a variation in a specific gene. ***Genomics,*** however, describes how we interpret and act on information from the whole genome, or any part of it. The National Genomic Test Directory (https://www.england.nhs.uk/publication/national-genomic-test-directories/) refers to all tests as 'genomic' and we will do the same throughout this resource.

Look at the graphic to see the names of some genomic tests used in family planning or pregnancy. There is more information available here (https://www.genomicseducation.hee.nhs.uk/genomics-in-healthcare/genomics-in-midwifery/#toggle-id-7).

Our understanding of genomic information is increasing all the time. In addition, family histories change, and new information may alter clinical management or genetic risk assessment. If an expectant parent says something like "no-one was interested about this in my last pregnancy," consider revisiting this information – there could be cause for referral to clinical genetics for further testing. It is also always worth taking another look at a family history, especially if the previous genomics consultation was several years ago.

Figure 12.5. Pregnancy. Photo shows a pregnant individual's abdomen with hands making a heart sign over the abdomen. **Source:** Photo by Ignacio Campo, Unsplash license.

Referrals for genomic counselling or testing should be made at the earliest possible opportunity as the test results can provide information that can have a considerable impact on care. Some genomic tests can take several weeks to come back, so a fast referral is crucial. It is important to 'think genomics' whenever you ask about a personal, obstetric and family history, and to take timely, appropriate action if you notice a red flag.

Nurses working in labour and delivery may experience some of the following circumstances that require genomic literacy:

- A nurse could be the first to notice signs and symptoms that may indicate the baby has a genetic condition.
- A nurse could be involved in the delivery of a baby that was diagnosed with a genetic condition during the pregnancy or that has been identified as having a higher chance of having a condition, based on a screening test result or because of the family history.
- Nurses might be caring for an expectant parent who has a genetic condition themselves, meaning they are at higher risk during labour.

Table 12.2 Genetic conditions and the ways in which they can affect the pregnancy:

Condition	How it can affect the pregnancy
Loeys-Dietz or vascular Ehlers Danlos syndrome	Increased risk of uterine/vascular rupture.
Cystic fibrosis or sickle cell disease	Increased risk of complications around labour.
MCADD	Dietary considerations. Also has a considerable impact on neonatal care for the baby after birth (see our case study: Sara's story).
Haemophilia (carrier)	Increased risk of port-partum haemorrhage due to changes in factor VIII levels.
Marfan syndrome	Increased risk of complications around labour
Epidermolysis bullosa (EB)	Potential for huge changes in care and management, both during the pregnancy and neonatally. Read more in this document: 'Epidermolysis bullosa (EB) – information for pregnancy and childbirth' [PDF]
Factor V Leiden	Increased risk of clotting disorders in pregnancy, and of miscarriage. Autosomal dominant condition.

- Nurses could be involved in the delivery of a baby following termination of pregnancy, or a stillborn baby due to genomic complications.

Mental health

The challenge of the mind

Throughout the history of psychiatry, researchers have tried but failed to find any physical basis for the strikingly abnormal experiences and behaviours of patients with severe mental illness.

There are no blood tests or brain scans that can help us understand the nature of mental illness. Diagnoses are based on patterns in the clinical presentation, such as mood changes, delusions or ritualistic checking, and medications are prescribed on an empirical basis: we know that they work (sometimes with a surprising level of effectiveness), but we don't really know why.

Mental illnesses are especially difficult to research because invasive investigations of the brain are not possible in the way they are for other organs. Even when physiological differences *can* be measured, it is often impossible to distinguish whether these are causes or effects of mental illness.

Hope through research

It's now believed that our genes could well play a part in our susceptibility to any given illness, and the effect of genetics on the risk of schizophrenia and bipolar disorder are well evidenced and substantial.

Genomic research offers the hope of better understanding the root causes of mental illness: by finding specific genes which are involved in these devastating illnesses, we might gain some understanding of the pathological processes leading to their development and ultimately develop better treatments.

Figure 12.6 A colourful, computer-generated image of a brain in hues of blue, pink, and purple. **Source:** Photo by Milad Fakurian, Unsplash license

CNVs in schizophrenia

The discovery with the most immediate clinical relevance relates to schizophrenia. Research has found that some patients with the condition have a chromosomal abnormality called a copy number variant (CNV) – where there is either an extra copy of part of the chromosome (a duplication) or a part that is missing completely (a deletion).

There are around 12 known locations on the chromosome where a CNV results in a substantially increased risk of schizophrenia – perhaps a thirty-fold or more increase above the background risk of 1%. If such a CNV is present in a person with schizophrenia, then it would be reasonable to say that the CNV had 'caused' the illness.

Wider implications

Typically, a CNV will impact several different genes and it has proved difficult to identify which of these are specifically responsible for increasing risk. Nevertheless, discovering that a patient carries a CNV has important implications:

- Validation: Finding a CNV can provide the patient and those around them with a clear, concrete explanation for why they have become unwell. For many people, it can be difficult to accept that mental illness is real, and finding a definitive cause can help the person to understand and accept that their condition is valid and deserving of treatment.
- Associated conditions: As well as being the primary cause of a condition like schizophrenia, some CNVs

are also associated with increased risk of additional physical health conditions. Finding a CNV therefore presents an opportunity to investigate, and possibly discover, an illness that was previously undiagnosed.

- Impact on family: Any genetic diagnosis can also have implications for family members, and younger siblings of patients with schizophrenia often express anxiety that they may also develop the illness. If the patient carries a CNV but the sibling does not, then they can be reassured that they are at no increased risk.

The proportion of people with schizophrenia in which a CNV is found is small – around 2% – but since the identification of a CNV has important implications for them and their family, and since the test is simple and inexpensive, some psychiatrists argue that testing for CNVs should be routine for those with a new diagnosis.

Individual genes

It is known that when the function of certain genes is disrupted by variants in a person's DNA, the risk of schizophrenia can rise. However, implicating individual genes has proved challenging, and the first to be identified, *SETD1A*, did not provide insights into how its disruption might lead to schizophrenia, as had been hoped.

In 2019, research by an international collaboration called SCHEMA (https://www.sciencedirect.com/science/article/abs/pii/S0924977X17305096?via%3Dihub), analyzed thousands of exomes, and identified a handful of genes where loss of function substantially affects schizophrenia risk – with some genes appearing to be linked to disease processes.

The clearest example relates to a particular receptor molecule for the neurotransmitter glutamate. It was already known that drugs blocking this receptor, as well as a syndrome called autoimmune encephalitis where antibodies attack the receptor, could cause symptoms that are similar to schizophrenia. Researchers have now demonstrated that variants that disrupt a gene coding for this receptor also increase schizophrenia risk. Thus, pharmacological, immune and genetic results all suggest that impaired functioning of this glutamate receptor can increase the risk of developing psychotic symptoms and other problems associated with schizophrenia.

These findings offer an opportunity to try to develop better drug treatments which might modify receptor functioning and lessen symptoms.

Where we are now

Psychiatric genomics is a burgeoning area of research and ever-expanding clinical application. For example, the Psychiatric Genomics Consortium (https://pgc.unc.edu/) is a collaboration of over 800 international scientists working with the pooled data of almost 1 million participants to uncover the role of genetics in psychiatric disorders. Some other fascinating areas of implementation in this practice context include:

PharmGKB (https://www.pharmgkb.org/page/DrugUseAndAddiction) provides evidence-based

information and CPIC guidelines on pharmacogenomics for drugs, genes, and phenotypes involved in substance use disorder.

In this recent study published in November 2024, researchers used machine learning (AI) to detect complex structural variations in the genome that likely contribute to psychiatric disease.

The Mayo Clinic has a Psychiatric Genomics and Pharmacogenomics Program (https://www.mayo.edu/research/centers-programs/psychiatric-genomics-pharmacogenomics-program/focus-areas) that focuses on bipolar disorder, alcohol use disorder, and psychiatric pharmacogenomics.

Discoveries of genetic causes of disordered eating has led to advances in treatment and hope for patients who have been unsuccessful with more traditional therapies.

Neurology

Rapid advances in technology and understanding mean that genomic testing is becoming much more integral to the field of neurology. Understanding the control of gene expression in the brain is central to understanding normal brain function, and increasingly neurological disease.

As genomic technology is enabling progress in our understanding of the etiology of disease, it is enabling the development of new targeted therapies. Rapid progress in clinical trials and drug development are expected over the next few years. There are now trails underway for Parkinson's disease and motor neurone disease, for example, targeting specific genes such as *LRRK2* and *C9orf72*.

How is genomics used in neurology?

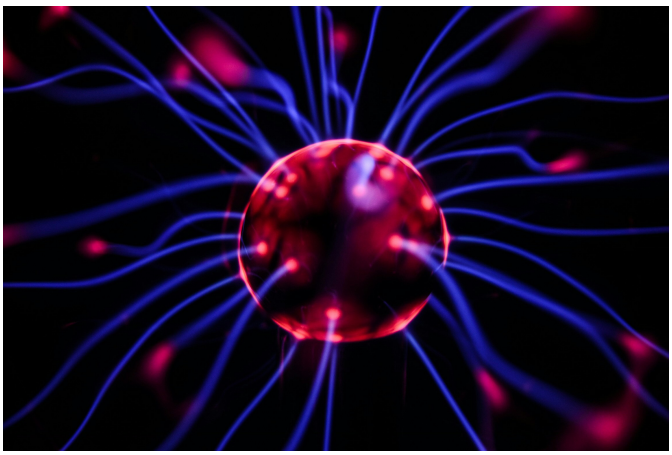

Figure 12.7. Photo by Josh Riemer on Unsplash

Diagnosis

Genomic testing is particularly useful in the diagnosis of familial and early-onset neurodegenerative diseases, for example ataxia, hereditary spastic paraparesis and some forms of dementia and Parkinson's. Disorders such as epilepsy can have a single genetic variant in about 30% of affected individuals (Jain et al., 2019), and more is becoming known about the genetics of neurodevelopmental disorders such as autism (Aldridge et al., 2024).

Predictive testing

Genomic test results can impact whole families. If variants are found early, it can enable better clinical management for the whole family and enable individuals to consider their options for the future. For example, identification of the Huntington's gene variant in a family with Huntington disease enables the counselling of other family members for risk-management including possible predictive testing and referral to relevant clinical trials.

Targeted treatment

In some instances, a precise genetic diagnosis means an individual can access gene-directed therapies which have a good chance of benefiting them.

Case Example: SMA

An example is the treatment of spinal muscular atrophy (SMA) with Nusinersin. It is hoped that other gene-directed therapies will soon be available.

- SMA is a rare, severely life-limiting and ultimately fatal neuromuscular condition which causes most affected children to die from respiratory failure within the first three years of life.
- Until 2016, there was no treatment for SMA and management in severe cases was with palliative care.
- SMA is caused by variants in the *SMN* gene, leading to loss of the SMN1 protein.
- In 2016, the therapy Nusinersin was introduced. Nusinersin works by upregulating a 'back-up' copy of the gene, *SMN2*.
- As a result of the availability of this therapy, children with a diagnosis who previously would have had a very limited life expectancy are able to lead much more normal lives.
- Although the long term effects of the treatment are not known, it is clear that it has a dramatic effect on both quality of life and life expectancy for affected children.

It is hoped that many more treatments, based on similar mechanisms, will be developed now that wider access to genomic technology and genomic data is possible.

Clinical trails and drug development

The identification of the genetic cause(s) of a disease makes it easier to develop targeted therapies. For example:

- The identification of variants in the synuclein gene in Parkinson's disease, and identifications and variants in the *APP* and presenilin genes in Alzheimer's disease (https://www.genetics.edu.au/SitePages/Alzheimer-disease.aspx), have allowed for the development of animal models. These animal models have been used to develop antibody-based treatments for these diseases, and those antibody treatments are now in clinical trials. Updates can be found on the Alzoforum website (https://www.alzforum.org/).
- Several years ago, the gene most commonly associated with motor neurone disease – the *C9orf72* gene – was identified. A gene therapy trial is now in progress, looking to turn off the abnormal gene and potentially provide a treatment for affected patients (see 'Genomics in Practice' example below).

The widespread availability and relative accessibility of genomic testing will result in more trials, more patients being eligible for and recruited to trials, and, as a result, more rapid progress in the area of targeted treatments.

Cardiology

The field of cardiology is increasingly influenced by advances in genomics, which can be used in diagnosis, treatment and management in a number of ways. Health professionals in cardiovascular medicine are increasingly likely to encounter genetic and genomic information and should be aware of how to deal with it.

As well as a role in rarer, inherited cardiac conditions, genomics is increasingly going to have a role in assessment and management of common cardiovascular diseases such as hypertension and coronary disease.

Genomic research directly identifies genes and pathways underpinning disease that may represent new therapeutic targets. Genetics and genomics also have an important and growing role in patient stratification.

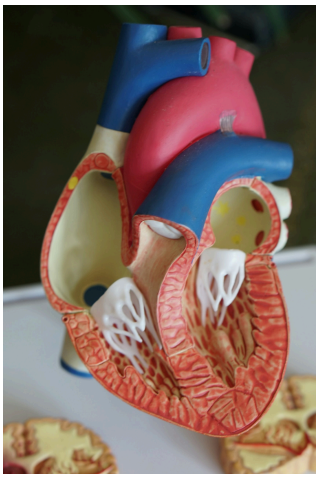

Figure 12.8. A plastic model of a heart, cut in half, displaying the four chambers, pulmonary, tricuspid and mitral valves, superior vena cava, pulmonary artery and aorta. **Source:** Photo by Robina Weermeijer, Unsplash license

Families with inherited cardiac conditions (ICC)

Most ICCs are autosomal dominant, meaning that immediate family members have a 50% chance of inheriting the same condition. Cascade testing can be used to determine the risk to the patient's family members.

Treatment and management of cardiac conditions

For some inherited cardiac conditions, treatment can be refined when we understand the precise molecular

basis of an individual's condition. For example, those with inherited arrhythmia may receive treatment tailored to the genetic cause.

Increasingly, other cardiological treatment can be chosen in accordance with an individual's genetics. For example, genetic testing can determine whether an individual will be resistant to clopidogrel, or has an elevated risk of developing statin myopathy.

Genetic information can be used to intervene early. For example, adopting a favourable lifestyle has been shown to reduce coronary disease risk by around 50% even in the presence of a high genetic predisposition.

To read some examples of Canadian nurses conducting research on the psychosocial aspects of participating in predictive genetic testing for cardiovascular conditions or living with autosomal dominant cardiac conditions, read Manuel and Brunger (2015) (https://journals.sagepub.com/doi/full/10.1177/2333393616674810)and Manuel and Brunger (2014) (https://doi.org/10.1007/s10897-014-9733-4).

New therapies

Understanding the genetic basis of disease can give us an insight into the molecular mechanisms and pathways involved, which can allow us to develop new treatment strategies. For example, specific disease-modifying targeted therapies are in phase 3 trials in both dilated and hypertrophic cardiomyopathies.

Inherited conditions can serve as genetic models for more common forms of disease. For example, PCSK9 inhibitors – a new class of lipid lowering therapy – were developed as a result of studies into familial hypercholesterolaemia.

New genome technologies are also offering the promise of new therapies through gene repair or replacement. Additional resources for cardiogenomics include GECKO (https://www.geneticseducation.ca/resources-for-clinicians/cardiogenomics) and the University of Ottawa Heart Clinic (https://www.ottawaheart.ca/heart-condition/inherited-cardiac-conditions-genetic-disorders).

Attribution & References

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12.5 UNIT SUMMARY AND REVIEW

Key Takeaways

This unit explored the interaction between environmental and genetic factors in shaping health outcomes, emphasizing the undeniable evidence of climate change and its direct and indirect impacts on physical, mental, and social health. Climate-related phenomena like forest fires, floods, and warming oceans have profound effects, including exposure to toxins, food chain disruptions, and economic challenges. Global pandemics, driven by environmental degradation, further highlight the interconnected nature of ecosystems. The WHO's 2022 report outlines recommendations for leveraging genomic technologies in global health, including pathogen surveillance, tracking antimicrobial resistance, studying disease outbreaks, and addressing health disparities through genomics.

The molecular and genomic underpinnings of cancer were explored, highlighting two physiological processes of cancer development: growth signal autonomy and insensitivity to growth inhibitory signals. Oncogenes, like *ras*, act as accelerators of cell division when altered by a variant, while tumor suppressor genes, such as *p53* and *BRCA1*, serve as brakes but can promote cancer when inactivated. Most cancers arise from acquired somatic variants, although germline variants, like those in *BRCA1* or Lynch syndrome genes, can elevate cancer risk. That is to say cancer cannot be inherited – one can inherit an increased risk of developing particular cancers. Advances in genomics, such as liquid biopsies and tumor genome sequencing, are transforming cancer detection, monitoring, and treatment. Nurses play a vital role in recognizing hereditary cancer risks, facilitating referrals, and advancing genomic literacy within oncology care.

The integration of genomics into clinical practice is advancing across several specialties, with oncology leading the way and growing applications in pediatrics, maternity, mental health, neurology, and cardiology, as examples. In these practice areas, genomic testing aids in diagnosis, guides treatments, and enables personalized interventions. It also facilitates family planning through cascade testing and genetic counseling. In psychiatry, genomic research has deepened

understanding of mental illnesses like schizophrenia and informed targeted therapeutic approaches. As genomics becomes more central to healthcare, practitioners must develop genomic literacy to meet evolving patient needs effectively.

Optional Additional Readings

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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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