Journalist Handbook
Special Focus on Neuroendocrine Tumors (NET)

Note: This handbook is provided by Novartis Pharmaceuticals Corporation and is intended for use by ex-US journalists to assist with reporting on neuroendocrine tumors.
# Neuroendocrine Tumors (NET): A Rare Cancer

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### Novartis and NET

Novartis has a long heritage in the research, development and discovery of treatments for NET. The company’s commitment to advancing the science in NET comprises research to better understand tumor biology; identification of better detection and diagnostic approaches and innovative treatments that improve patient outcomes. Novartis also supports the NET community by increasing disease awareness among healthcare professionals and the general public, improving patient services and education, and collaborating closely with researchers, patient groups, clinicians and professional societies. Due to our heritage, commitment and expertise in NET, we are providing this resource to help journalists understand the basics of this rare disease.
Neuroendocrine Tumors (NET): A Rare Cancer

As we begin our overview of neuroendocrine tumors (NET) – it is important to provide a brief summary of the neuroendocrine system. The neuroendocrine system includes a network of cells distributed throughout the body that produce and release hormones. These hormones travel through the bloodstream to tissues or organs, affecting body processes from head to toe, such as regulating the air and blood flow through the lungs and controlling the speed at which food is moved through the gastrointestinal (GI) tract.

Like all cells, neuroendocrine cells are always growing, dying and being replaced by new cells. Sometimes, neuroendocrine cells do not grow the way they are supposed to. This is when tumors may form. Tumors of the neuroendocrine system are called NET, which may also be called neuroendocrine cancer.

Recent data show that in 2004, NET were diagnosed in approximately 5.25 cases per 100,000 people. The incidence of NET has increased five-fold in the past 30 years, which is mostly driven by an escalation in rectal and gastric NET. People with a family history of cancer, women and those with diabetes are at an increased risk of developing NET.

NET can be categorized as either symptomatic or asymptomatic (also known as functional or non-functional). Symptomatic NET are also known as carcinoid tumors. Patients with symptomatic NET may experience clinical symptoms due to the excess release of hormones from the tumor cells. The symptoms vary based on the type of NET the patient has (e.g., GI NET may result in diarrhea and/or abdominal pain, while lung NET may result in coughing and/or wheezing).

The amount of time a patient can live with NET varies depending on the stage of the disease. For patients diagnosed with grade 1 or grade 2 NET (low or intermediate grade), median survival is 124 and 64 months respectively; however, the median survival for patients diagnosed with grade 3 NET (high-grade) drops to 10 months. Patients with functional NET typically have a five year survival rate of less than 50%.
Different Types of NET

Gastrointestinal (GI) NET
Gastrointestinal (GI) NET are the most common type of NET. They start in different parts of the digestive system, which includes the stomach, small intestine, colon, and rectum. GI NET can be categorized as functional, which cause symptoms because they make large amounts of hormones or non-functional, which may not have symptoms or may produce symptoms caused by the tumor’s growth, such as intestinal blockage, pain, and bleeding.

Most of the time, GI NET are small and hard to find. Sometimes non-functioning NET are found during other procedures like a colonoscopy or gastroscopy, or surgery for other diseases. Symptomatic NET may be difficult to diagnose because they can cause symptoms that are similar to those of other GI diseases such as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). Nighttime diarrhea is an important clue for doctors that a patient may have a GI NET.

GI NET accounts for 61% of NET diagnoses. Recent data show that in 2004, 5%–44% of patients with GI NET had advanced disease at time of diagnosis. Survival rates vary based on the specific site of origin of the tumor in the GI tract. The 5-year survival for NET of the small intestine was 86.2%, 82.7% for stomach, and 67.4% for colon.

Lung NET
Lung NET are a rare form of lung cancer, making up about 2% of all lung tumors and 25% of all types of NET. Two types of lung NET include typical carcinoid (low grade) and atypical carcinoid (intermediate grade). Lung NET start in the lungs, but can spread to the outer area of the lungs and beyond. Two rare but serious types of lung NET are called small cell lung carcinoma and large cell neuroendocrine carcinoma of the lungs. They may also be called grade 3 (G3) tumors.

Lung NET are different from other types of lung cancers, typically growing more slowly. Doctors may refer to these tumors as lung carcinoids or bronchial NET. Some lung NET cause symptoms that make them seem like other respiratory diseases (e.g., coughing, wheezing), while others do not cause any symptoms. In fact, the majority of lung NET do not produce hormones.

Recent data show that in 2004, lung NET were diagnosed in approximately 1.35 cases per 100,000 people. At time of diagnosis, approximately 28% of patients with lung NET had advanced disease. The 5-year survival rate for localized lung NET is 84% whereas the 5-year survival rate for patients with advanced lung NET is 27%. Delays in diagnosis can also lead to progressive disease, meaning that the cancer is growing, spreading or getting worse.

Pancreatic NET
Another type of NET originate in the pancreas. Pancreatic NET are different from and much less common than pancreatic exocrine cancer, which is generally referred to as pancreatic cancer. Similar to the other types of NET, pancreatic NET can be categorized as either symptomatic (functional) or asymptomatic (non-functional). Patients with functional pancreatic NET may experience clinical symptoms due to the excess release of hormones from the tumor cells. For example, some pancreatic neuroendocrine cells may secrete excess gastrin, a hormone that causes the stomach to produce too much acid, leading to stomach ulcers which can cause pain, nausea and decreased appetite.

Recent data show that in 2004, pancreatic NET were diagnosed in approximately .32 cases per 100,000 people. At time of diagnosis, approximately 64% of patients with pancreatic NET had advanced disease. The 5-year survival rate for localized pancreatic
NET is 79% whereas the 5-year survival rate for patients with advanced pancreatic NET is 27%\(^3\).

**Mechanism of Disease**

The endocrine system is made up of cells that make hormones. Hormones are chemical substances that are produced by the body and carried through the bloodstream to have a specific effect on the activity of other organs or cells in the body\(^2\).

A tumor begins when normal cells change and grow uncontrollably, forming a mass. An endocrine tumor is a mass that begins in the parts of the body that produce and release hormones. Because an endocrine tumor develops from cells that produce hormones, the tumor itself can produce hormones and cause serious illness\(^2\).

A malignant transformation of NET begins in the hormone-producing cells of the body’s neuroendocrine system. The neuroendocrine system is made up of cells that are a cross between traditional hormone-producing endocrine cells and nerve cells. These cells are the building blocks of the nervous system. Neuroendocrine cells are found throughout the body in organs such as the lungs and gastrointestinal tract, including the stomach and intestines. The type of NET a patient has is based on where the NET originates in the body (e.g., pancreas, GI tract, lungs)\(^5\).

**Clinical Manifestations**

NET can secrete hormones and peptides that may cause distinct clinical manifestations. Some of the symptoms and syndromes associated with NET are due to excessive secretion of these hormones and other bioactive substances. Other NET symptoms are due to tumor size or growth\(^20\).

**Signs & Symptoms**

Signs and symptoms of NET may include, but are not limited to\(^2\):
- Abdominal pain/cramping
- Diarrhea/steatorrhea (excess fat in the stools)
- Constipation
- Anorexia, nausea, vomiting
- Persistent cough or wheezing
- Loss of appetite or weight loss
- Persistent pain in a specific area
- Unusual bleeding or discharge
- Hyperglycemia
- Hypoglycemia
- Dermatitis

Carcinoid syndrome is a set of symptoms that can arise from advanced, functioning GI NET that produce excess hormones, occurring in 8% to 35% of patients\(^21\). Carcinoid syndrome is frequently associated with neoplasms (abnormal tissue masses, or tumors) of the midgut, which frequently metastasize\(^21\). The most common signs and symptoms experienced by patients with carcinoid syndrome are flushing, diarrhea, abdominal cramping and cardiac disease caused by valvular heart lesions\(^22\).
Diagnosing NET

A diagnosis of NET can take an estimated five to seven years, and even symptomatic patients may be misdiagnosed since symptoms can be similar to other diseases and conditions (e.g., irritable bowel syndrome)\textsuperscript{2,23}.

Since NET are rare, and can occur in various places throughout the body, there is no routine screening; however, computed tomography (CT) scans, magnetic resonance imaging (MRI), ultrasound endoscopy and somatostatin receptor scintigraphy are common tools used to diagnose NET once it is suspected\textsuperscript{2,8}. Also helpful in diagnosing NET are blood and urine tests that evaluate biomarkers. Selected biomarkers are chromogranin A (CgA) or 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA), a by product of serotonin, which is produced by carcinoid tumors\textsuperscript{2}.

Disease Management and Multidisciplinary Care

There are many considerations involved in determining a treatment plan for a patient with NET, including whether the cancer has spread to other parts of the body, as well as the patient's overall health\textsuperscript{2}. Current therapeutic options include surgery, radiation therapy, chemotherapy and medical therapies\textsuperscript{24}.

The appropriate treatment and management of NET is dependent on a variety of factors, such as\textsuperscript{2,8}:

- Location of tumor and specific glands involved
- Grade of tumor
- Differentiation of tumor cells
- Aggressiveness and stage of tumor
- Amount of hormones produced
- Specific patient needs
- Comorbidities/clinical manifestations involved

NET may require collaboration among specialists from multiple disciplines, given the nature of the disease\textsuperscript{2}. Research suggests that patients with NET should be evaluated and managed by a team of specialists in multiple disciplines\textsuperscript{6,8}.

The multidisciplinary team may include\textsuperscript{8}:

- **Oncologist** (specializes in treating cancer)
- **Endocrinologist** (specializes in the diagnosis and treatment of disorders of the endocrine system)
- **Gastroenterologist** (specializes in diagnosing and treating disorders of the digestive system)
- **Interventional radiologist** (specializes in creating and interpreting scans of areas inside the body)
- **Nuclear medicine expert** (works with medicine that uses small amounts of radioactive substances to highlight various processes and markers inside the body that ultimately inform how to treat a disease)
- **Nurse** (trained to care for people who are ill or disabled)
- **Pathologist** (identifies diseases by studying cells and tissues under a microscope)
- **Surgeon** (removes or repairs a part of the body by operating on the patient)
- **Dietitian** (a health professional with special training in nutrition who can help with dietary choices)
- **Pulmonologist** (specializes in treating diseases of the lungs)
- **General practitioner** (treats acute and chronic illnesses and provides preventive care and health education to patients)
Global NET Survey

A collaboration between the International Neuroendocrine Cancer Alliance (INCA) and Novartis Pharmaceuticals Corporation, the Global NET Survey was the first global survey of patients with NET that aimed to increase understanding of the experiences, needs and challenges of patients with NET and learnings among countries and regions to advance NET care.

From February through May 2014, 1,928 respondents from 12 countries who reported that they were diagnosed with NET participated in a 25-minute online survey, available in eight languages. Participants were recruited by INCA member organizations through flyers, website postings, e-mails, social media and other channels. The survey was funded by Novartis. Hall & Partners, a communications research agency, fielded and analyzed the results.

The Global NET Survey had limitations that may have impacted results:

- A patient-reported design was employed without independent verification, leading to potential recall bias
- Life quality was evaluated using a multiple choice questionnaire and did not utilize standardized, validated quality-of-life assessments
- Recruitment was conducted primarily through patient advocacy groups (37%) and online sources (51%), which may have resulted in a potentially biased sample not fully representative of the heterogeneous NET patient population
- Respondents were more likely to be highly engaged and motivated care seekers, including female patients and/or those with a poorer prognosis

Results related to the burden of disease indicated that:

- NET has a moderate to significant negative impact on 71% of patients’ lives
- 92% of respondents made a lifestyle change as a result of their NET
- 56% of patients experienced general fatigue, muscle fatigue and weakness due to their NET

Survey results demonstrated the benefits patients felt in receiving care from a multi-disciplinary team (MDT), including improved satisfaction with their care and interaction with the healthcare professionals (HCPs) managing their cancer. Survey respondents who visited a NET specialist center reported discussing a broader range of NET-related topics with their HCPs compared to those who did not, including results of ongoing tests, changes in symptoms and overall well-being. Respondents with a MDT reported better relationships with their HCPs compared to those who did not have a MDT.

Regarding the diagnosis process, respondents reported seeing an average of six HCPs prior to their NET diagnosis, with 25% of patients being diagnosed for NET as a result of being tested for something else. Almost half (45%) of respondents said they did not receive NET as the initial diagnosis. Respondents also agreed (71%) with the statement that there is a lot of room for improvement in the process of diagnosing NET. This includes receiving clearer information on long-term impact (60%) and more immediate access to HCPs with NET expertise (53%).

Overall, respondents reported that improved access to NET treatments and a NET medical team, increased awareness of NET, and a better understanding of how to manage disease-related symptoms would help them to live a better life.
Selected Resources

This section provides an overview on where to obtain credible information regarding NET.

Medical Literature Databases

- Thomson Reuters: http://science.thomsonreuters.com/mjl
- Thomson Reuters:
  http://science.thomsonreuters.com/mjl

Clinical Trial Databases

- Clinical Trials (US): http://www.clinicaltrials.gov
- International Clinical Trials Registry Platform (WHO): http://www.who.int/ictrp

Government Agencies & Resources

- National Institutes of Health Office of Rare Diseases Research (US): http://www.rarediseases.info.nih.gov
- US Food and Drug Administration (US): http://www.fda.gov
- World Health Organization: www.who.int

Professional Medical Organizations

- Cancer Research UK (UK): http://www.cancerhelp.org.uk
- European Neuroendocrine Association: http://www.eneassoc.org
- European Neuroendocrine Tumor Society: http://www.enets.org

Patient Organizations and Resources

- International Neuroendocrine Cancer Alliance: http://www.incalliance.org
- APOZ & Friends (Bulgaria): http://www.oncobg.info
- APTED, L’Association des Patients porteurs de Tumeurs Endocrines Diverses (France): http://www.apted.fr/
- Bundesorganisation Selbsthilfe NeuroEndokrine Tumoren e.V. (Germany): http://www.net-shg.de
- Carcinoid & Neuroendocrine Tumor Society (CNETS Singapore): http://www.cnets.org/
- CarciNor, foreningen for personer med neuroendokrin kreft (Norway): http://www.carcinor.no/
- Carcinoid-Neuroendocrine Tumor Society (CNETS Canada): http://www.cnetscanada.org
- CARPA The Carcinoid Patient Association (Sweden): http://www.carpapatient.se/
- Espaço de Vida (Brazil): http://www.espacaodevida.org.br
- Kooperativní skupina pro neuroendokrinní nádory (Czech Republic): http://www.neuroendokrinni-nadory.cz
- NET Fenix (Colombia): http://www.asociacionnetfenix.blogspot.com
- NET Italy: http://www.netitaly.net
- NET Patient Foundation (UK): http://www.netpatientfoundation.org
- Netpa (Denmark): https://www.cancer.dk/netpa/forside/
- Netzwerk Neuroendokrine Tumoren (NeT) e. V. (Germany): http://www.glandula-net-online.de/
- Neuroendocrine Cancer Awareness Network (US): http://carcinoidawareness.org
- Stichting NET- Groep (The Netherlands): http://www.net-kanker.nl
- Stowarzyszenie Pacjentów i Osób Wspierających Chorych na Guzy Neuroendokrynne (Poland): www.rakowiak.pl/statut.htm
- The Carcinoid Cancer Foundation (US): http://www.carcinoid.org
- The Hope Society for Cancer Care (Taiwan): http://www.ecancer.org.tw
- The NET Alliance: A Novartis Oncology Initiative: http://thenetalliance.com
- Unicorn Foundation (Australia/New Zealand): https://www.unicornfoundation.org.au
**NET Glossary**

**Key terms for use in interpreting information and developing stories on neuroendocrine tumors:**

**Appendix:** A small, fingerlike pouch that sticks out from the cecum (the first part of the large intestine near the end of the small intestine).

**Asymptomatic:** Having no signs or symptoms of disease.

**Atypical lung carcinoid:** A type of lung NET that grows a little faster and is somewhat more likely to spread to other organs compared to typical lung carcinoid. They have more cells in the process of dividing and look more like a fast-growing tumor. They are much less common than the typical lung carcinoids.

**Carcinoid tumor:** A slow-growing type of tumor usually found in the gastrointestinal system, and sometimes in the lungs or other sites in the body. Carcinoid tumors may spread to the liver or other sites in the body, and they may secrete substances such as serotonin or prostaglandins, causing carcinoid syndrome.

**Carcinoid syndrome:** A combination of symptoms caused by the release of serotonin and other substances from carcinoid tumors of the gastrointestinal tract. These may include flushing of the face, diarrhea, bronchial spasms, rapid pulse and sudden drops in blood pressure.

**Chromogranin A (CgA):** A protein found inside neuroendocrine cells, which release CgA and certain hormones into the blood. CgA may be found in higher than normal amounts in patients with certain types of NET, small cell lung cancer, prostate cancer and other conditions. Measuring the amount of CgA in the blood may help to diagnose the cancer or other conditions or find out how well treatment is working or if cancer has come back. CgA is a type of tumor marker.

**Comorbidity:** The condition of having two or more diseases at the same time.

**Computerized tomography (CT) scan:** A computer imaging method that uses x-rays to create three-dimensional pictures of areas inside the body.

**Differentiation:** The processes by which immature cells become mature cells with specific functions. Describes how much or how little tumor tissue looks like the normal tissue it came from. Well-differentiated cancer cells look more like normal cells and tend to grow and spread more slowly than poorly differentiated or undifferentiated cancer cells. Differentiation is used in tumor grading systems, which are different for each type of cancer.

**Endocrine system:** A system of glands and cells that make hormones that are released directly into the blood and travel to tissues and organs throughout the body. The endocrine system controls growth, sexual development, sleep, hunger and the way the body uses food.

**Functional:** Characterized by producing symptoms related to the excess release of hormones from tumor cells. Also known as symptomatic.

**Gastrin:** A hormone released from cells in the lining of the stomach after eating, which causes the stomach digest food.

**Gastrointestinal NET:** A slow-growing cancer that forms in cells that make hormones in the lining of the gastrointestinal tract. It usually occurs in the small intestine, rectum, or appendix. A gastrointestinal NET may increase the risk of forming other cancers of the digestive system.

**Gastrointestinal tract:** The stomach and intestines. The gastrointestinal tract is part of the digestive system, which includes the salivary glands, mouth, esophagus, liver, pancreas, gallbladder and rectum.

**Hormone:** Chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs.

**Large cell lung carcinoma:** A lung cancer in which the cells are large and look abnormal under a microscope.

**Large intestine:** A long, tube-like organ that is connected to the small intestine at one end and the anus at the other. The large intestine has four parts: cecum, colon, rectum and anal canal.
**Lung NET:** A NET that originates in the lungs. Lung NET may also be referred to as lung carcinoids or bronchial NET\(^7\).

**Magnetic resonance imaging (MRI):** A non-invasive diagnostic technique that produces computerized images of internal body tissues and is based on nuclear magnetic resonance of atoms within the body induced by the application of radio waves\(^2\).

**Malignant:** Cancerous. Malignant cells can invade and destroy nearby tissue and spread to other parts of the body\(^7\).

**Metastasize:** To spread from one part of the body to another\(^7\).

**Neoplasm:** An abnormal mass of tissue that results when cells divide without control. A neoplasm can also be referred to as a tumor\(^7\).

**Neuroendocrine system:** Relating to the interactions between the nervous system and the endocrine system. The neuroendocrine system is made up of cells that release hormones into the blood in response to a stimulation of the nervous system\(^7\).

**Neuroendocrine tumor:** A tumor that forms from cells that release hormones into the blood in response to a signal from the nervous system\(^7\).

**Non-functional:** Characterized by tumors that may produce symptoms but do not have a specific set of symptoms. Also known as asymptomatic\(^6,11\).

**Pancreatic cancer:** A cancer in which malignant cells are found in the tissues of the pancreas. This disease is also referred to as exocrine cancer\(^7\).

**Pancreatic NET:** A tumor that forms in the hormone-making cells of the pancreas, which make several different hormones that affect bodily functions\(^7\).

**Peptides:** A molecule that contains two or more amino acids, which join together to form proteins\(^7\).

**Serotonin:** A hormone found in the brain, blood platelets and central nervous system that acts as a neurotransmitter. A lack of serotonin in the brain is associated with depression\(^7\).

**Small cell lung cancer:** A fast-growing cancer that forms in tissues of the lung and can spread to other parts of the body\(^7\).

**Small intestine:** A long tube-like organ that connects the stomach and the large intestine. It folds many times to fit inside the abdomen. The small intestine has three parts: the duodenum, jejunum, and ileum\(^7\).

**Somatostatin:** A natural peptide hormone secreted in various parts of the human body, including the digestive tract, able to inhibit the release of numerous endocrine hormones, including insulin, glucagon and gastrin\(^2\).

**Somatostatin receptor scintigraphy (SRS):** A type of scan used to find carcinoid tumors, creating pictures of where malignant cells are in the body. Somatostatin receptor scintigraphy can also be referred to as octreotide scan\(^7\).

**Stomach:** An organ that is part of the digestive system. The stomach helps digest food by mixing it with digestive juices and churning it into a thin liquid\(^7\).

**Symptomatic:** Having symptoms, which indicate signs of a condition or disease\(^7\).

**Tumor:** An abnormal non-cancerous or malignant new growth of tissue that possesses no physiologic function and arises from uncontrolled usually rapid cellular proliferation\(^7\).

**Tumor grade:** A description of a tumor based on how abnormal the cancer cells and tissue look under a microscope and how quickly the cancer cells are likely to grow and spread. Low-grade cancer cells look more like normal cells and tend to grow and spread more slowly than high-grade cancer cells\(^7\).

**Typical lung carcinoid:** A type of lung NET that tend to grow slowly and only rarely spread beyond the lungs\(^17\).
Commonly Used Terms

The following terms frequently appear in journal articles and conference presentations:

**Statistical Terms**

**Confidence interval (CI):** Describes how precise a particular result is and suggests how reliable it may be beyond the specific study. In a clinical trial, the CI indicates the limits within which the difference between two treatments is likely to lie. CIs are reported as a range of values above and below the study finding; the more narrow the range, the more precise the result. For example, a disease that is present in 25 percent of a population with a CI of plus or minus 5 percent means that the actual value can lie anywhere between 20 and 30 percent.

**Mean:** The sum of a set of numbers divided by how many numbers are in the set. In a clinical study, there will always be patients who will fall above or below the mean.

**Median:** The middle value in a set of measurements.

**P-value (probability value):** A measure of probability that a difference between groups during an experiment happened by chance. For example, a p-value of .01 (p=0.01) means there is a 1 in 100 (1 percent) chance the result occurred by chance. In a clinical trial, the lower the p-value, the more likely it is that the difference between groups was caused by the treatment being studied.

**Statistical significance:** Results that are statistically significant are unlikely to be due to chance. A p-value less than 0.05 (meaning that the result would have arisen by chance on less than one occasion in 20) is generally considered statistically significant. In clinical trials, the level of statistical significance depends on the number of participants studied and the observations made, as well as the magnitude of differences observed.

**Clinical Trial Terms**

**Blinded trial:** A study in which the patients (single-blinded) or the patients and their doctors (double-blinded) do not know which drug or treatment is being given; the opposite of an open-label study.

**Clinical trial:** A research study that tests the effectiveness and safety of medications, devices and/or treatment paradigms in humans.

- **Phase I clinical trial:** Initial studies conducted with a small number of volunteers with or without the disease (can be fewer than 80) to assess the safety and various dose ranges for an experimental treatment.

- **Phase II clinical trial:** Mid-stage studies (which occur after a Phase I trial) typically involving a larger number of patient volunteers to further assess safety and effectiveness of an experimental treatment.

- **Phase III clinical trial:** Large trials (which occur after Phase II) carried out to confirm the effectiveness of an experimental treatment and identify adverse events. Phase III trials are conducted to compare an experimental treatment to commonly used treatments, and collect information to evaluate the overall risk/benefit ratio. Phase III trials provide the basis for applications with regulatory agencies for authorization to market a new drug.

- **Endpoint:** An overall measurable outcome that the study is designed to evaluate. The primary endpoint(s) measure outcomes related to the main objective of the study and secondary endpoints evaluate measures for other related questions in the study.
**Non-inferiority trial:** A study intended to show that the effect of a treatment is not worse than that of an active control, by no more than a specified range.\(^{31}\)

**Open-label trial:** A study in which both the patients and the doctors know which treatment is being given; opposite of a blinded study.\(^{30}\)

**Post-hoc analysis:** An examination of data, after a clinical trial has concluded, for analyses that were not previously specified.\(^{32}\)

**Prospective trial:** A study or clinical trial in which participants are identified and then followed forward in time.\(^{7}\)

**Randomized trial:** A study in which the participants are assigned by chance to separate groups that compare different treatments. Large, randomized, double-blind, controlled prospective clinical trials are considered to provide the highest quality of scientific evidence.\(^{7}\)

**Retrospective study:** A study that compares patients with the disease or condition under study (cases) and a similar group of people who do not have the disease or condition (controls). Researchers study the medical and lifestyle histories of the people in each group to learn what factors may be associated with the disease or condition. A retrospective study is also called a case-control study.\(^{7}\)
References


