



PERU: CLINICAL RESEARCH AND EPIDEMIOLOGIC INFORMATION – INNOVATING IN HEALTH

NATIONAL ASSOCIATION OF PHARMACEUTICAL LABORATORIES



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INFORMATION - INNOVATING IN HEALTH

Clinical Research Committee

NATIONAL ASSOCIATION OF PHARMACEUTICAL LABORATORIES
(ALAFARPE)

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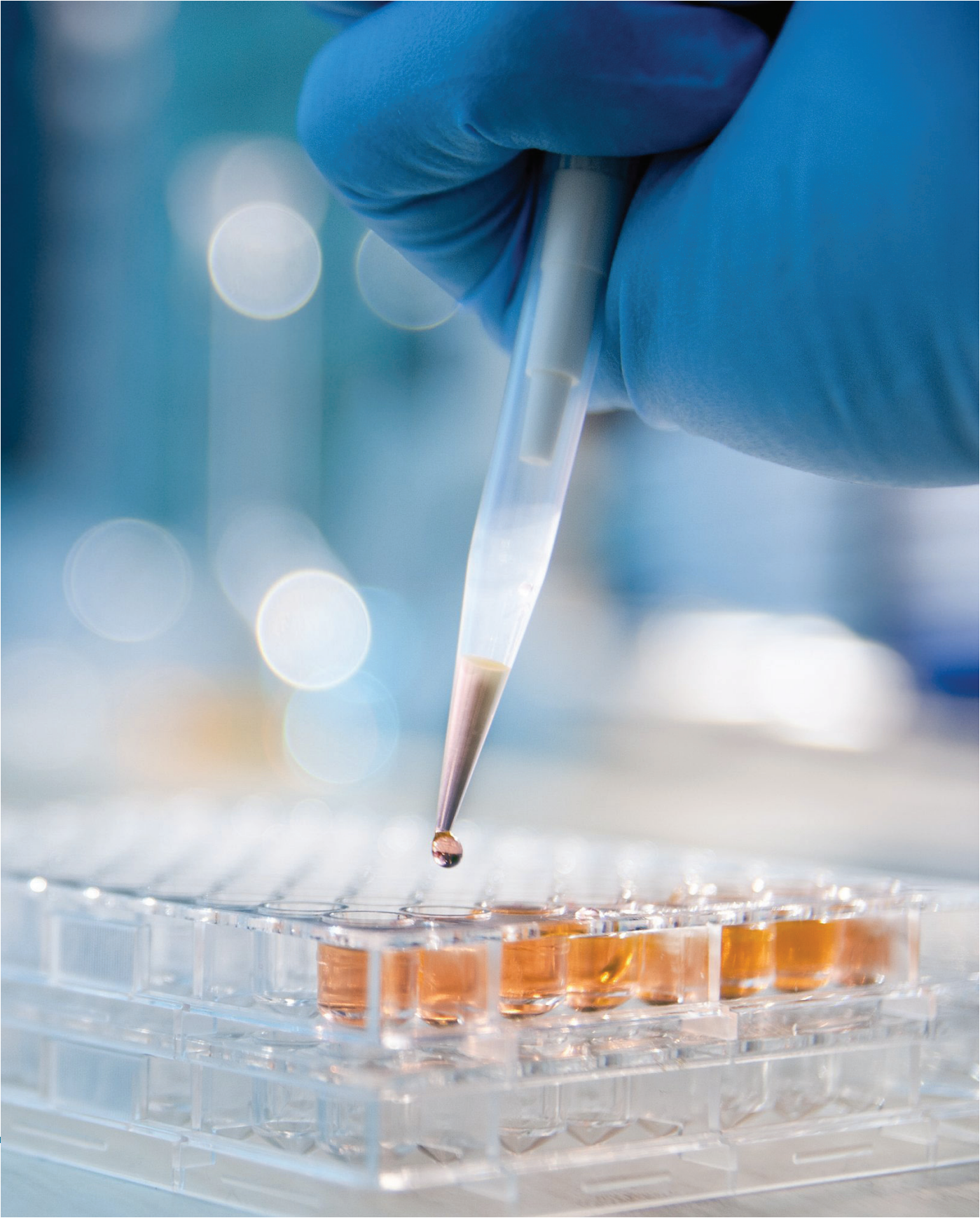
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San Isidro
Lima 27 - Perú

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According to the 2008 International Monetary Fund country report, Peru has had continued economic growth for the past two decades due to sound macroeconomic policies and structural reforms. After a difficult 2017, Peru's economy was expected to increase by 3.7% in 2018 and rise to over 4% in 2019-2020 because of political and economic stability. Peru has more than 32 million inhabitants from various ethnic groups, and is experiencing an epidemiological transition with the double burden of communicable and non-communicable diseases. Which are common to developing and developed countries.

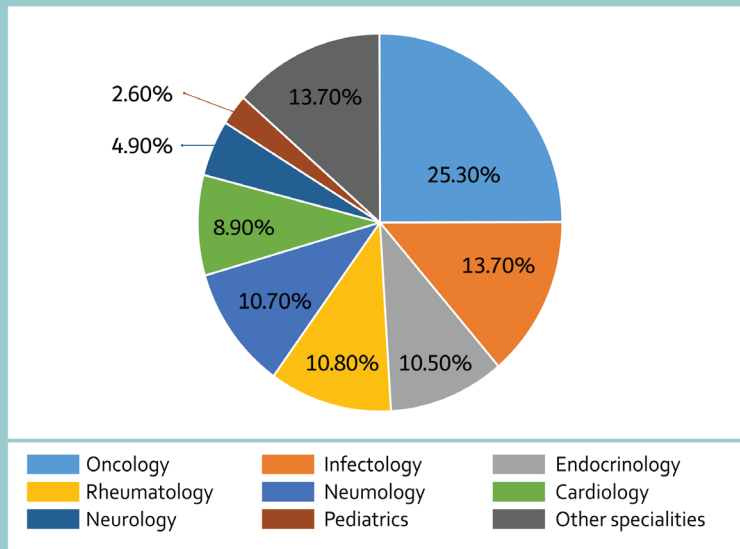
To improve their diagnosis, prevention and treatment, it is necessary to obtain the best available evidence related to these diseases. For this, it is important to have a continuous and dynamic feedback loop involving three components: first, basic knowledge about the disease; second, procedures to develop more effective treatments including new technologies and third, the adoption of effective practices to treat the disease. This is how new treatments are identified; while some prove to be effective and are integrated into practice, others turn out to be less effective or ineffective, which may be modified or simply not used. Clinical trials are conducted to increase the knowledge of treatment, diagnosis and prevention of diseases or conditions.

Since 1995, 1,668 clinical trials were approved to be performed in Peru, and from 2006 to 2018, 1,102 clinical trials. The main medical specialties in which clinical trials are done include oncology, infectology, endocrinology, rheumatology and neumology.

In Peru, as in many other countries, the majority of clinical trials are funded by pharmaceutical companies such as: Amgen, AstraZeneca, Bristol-Myers Squibb (BMS), Gilead, GlaxoSmithKline (GSK), Janssen, Merck (known as MSD outside the U.S.), Novartis, Pfizer, Roche and Sanofi. However, approximately 12% of clinical trials conducted in the country are funded by universities, foundations and national and international governmental agencies. These include: Universidad Peruana Cayetano Heredia (Lima), Universidad Mayor de San Marcos (Lima), John Hopkins

Graphic 1

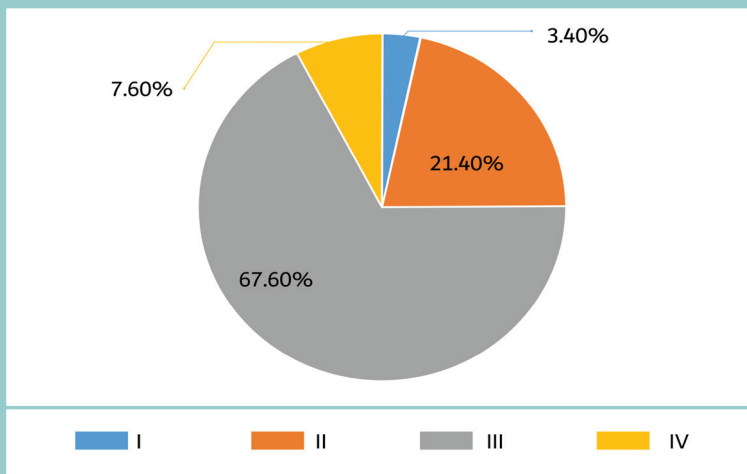
Peru: Approved clinical trials from 2006 to 2018 by speciality, n=1102



In Peru, Phase III trials are the most common followed by Phase II.

Graphic 2

Peru: Approved clinical trials between 2006 to 2018 by study phase, n=1102



University, Prisma (Lima), the *Eastern Cooperative, Oncology Group* (ECOG) and the U.S. National Institutes of Health (NIH).

Planning a clinical trial requires, in first place, the knowledge of epidemiologic health characteristics conditions to investigate, the incidence and the justification to perform the proposed study. This document summarizes the 2018 epidemiologic information of the health conditions from the clinical trials more frequently done in the country.

Also, it is important to stablish strategies to facilitate access to an opportune screening, early diagnosis and effective treatment for these health conditions. Certainly, it is in the effective treatment environment, in where the research in new drugs and therapies give us alternatives to improve the patient quality of life.

Policies and regulations

Since 2000, Peru has passed a series of policies regulating clinical trials mirroring international bioethics standards and good clinical practices. According to Article 28 of Law No. 26842, General Health Law, clinical trials must adhere to national and international legislation, and ethical guidelines including the Helsinki Declaration.

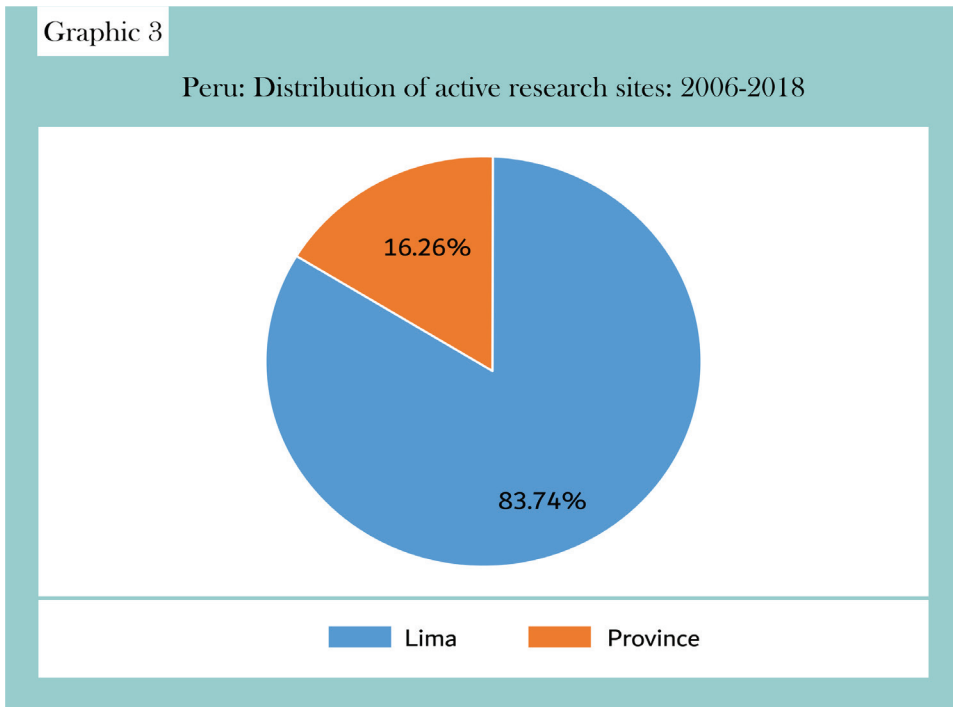
Good Clinical Practice (GCP) provides ethical and scientific standards for researchers, sponsors, monitors and ethics committees during all trial stages. These guidelines are used to submit information required by the Regulatory Authority, guarantee participant safety and well-being, maintain scientific integrity and objectivity, and establish responsibilities for those involved in the trial. Advances in clinical research and technology require compliance to GCP.

In Peru, The National Institute of Health is responsible for regulating clinical trials, and thereby responsible for ensuring compliance with the Clinical Trials Regulation (REC, acronym in Spanish) approved by Supreme Decree No. 021-2017-SA, and supporting regulations related to clinical trials. The General Office of Research and Technology Transfer (OGITT, acronym in Spanish) is responsible for the approval, surveillance and safety, and supervision of clinical trials including inspections.

Likewise, the OGITT is responsible for the Peruvian Registry of Clinical Trials

(REPEC, acronym in Spanish), which is a public registry of all approved clinical trials in the country (See <https://ensayosclinicos-repec.ins.gob.pe/> for more information). REPEC is certified by the International Clinical Trial Registry Platform (ICTRP) of the World Health Organization.

By national regulation both ethics committees, as research sites must be authorized by the National Health Institute (part of Ministry of Health) to execute actions related to clinical trials. According to REPEC platform for April 2019, Peru had 364 active research sites (between 80 to 85% in Lima city) and 20 active ethics committees certified by this regulatory entity. The national health institute also supervise their proper functioning, according to its annual program.



Clinical trials have been conducted in Peru for over 20 years, and have contributed to knowledge about the efficacy and effectiveness of treatments for prevalent diseases and health conditions. In addition, Peru has seen an increased investment in research and specifically clinical research, in the areas of infrastructure, human resources, bioethics, GCP, and technologies. While clinical trials have created public awareness regarding the need and relevance of research, there is a need to grow awareness and mutually beneficial relationships between scientific research and the diversity of communities in Peru.



Lima capital of Peru, seen from the sea.
In this city are the majority of research centers.



+ Breast cancer

Breast cancer is one of the most common cancers in Peru. In 2017 it was the third leading cause of death among all cancers (2.57% of total deaths in women of all ages), and was the leading cause of cancer-related death in women between 59 and 70 years (5.58% of total deaths in women in this age group). In addition, it is an important contributor to disease and economic burden and poor survival rates due to late diagnosis.

In Peru, the prevalence of breast cancer follows a growing trend: in 2006 it was 166 per 100,000 women; in 2010 it increased to 188, and in 2017 the prevalence was 212 per 100,000 women. The prevalence was higher in women between 50 and 69 years old: 672 per 100,000 women in 2017.

In 2017, the incidence rate of breast cancer in Peru was 27 new cases per 100,000 women, and was greater in women from 50 to 69 years, with 82 new cases per 100,000 women.

In 2010, breast cancer for women aged 15-49 represented 4.16% of total deaths, increasing to 4.84% in 2017. This is higher in women aged 50-69, representing 4.86% of total deaths in 2010, and increasing to 5.58% in 2017.

In Peru, it is estimated that in 2017 alone, 693,366 healthy life years (HLY) were lost to cancer, of which, 23,799 HLYs were from breast cancer, mainly due to premature mortality.

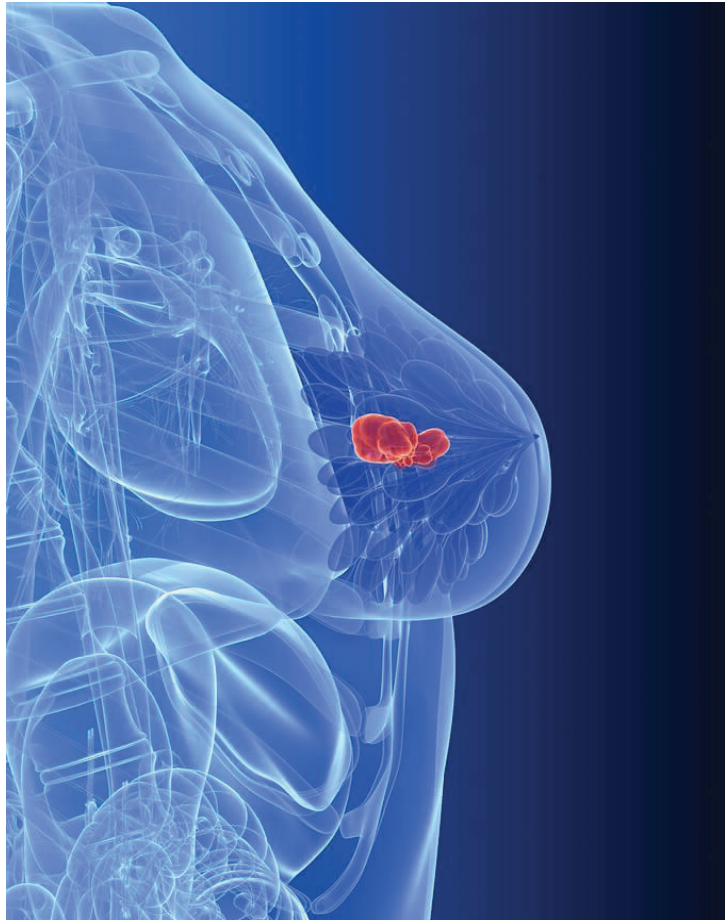
The overall 5-year survival rate of breast cancer among women has increased in the last three decades due to advancements in treatment options (chemotherapy, hormone therapy and targeted drug therapy), earlier detection due to increased awareness, and increased use of mammography.

As described in the clinical practice guidelines in oncology, breast cancer treatment options include local treatments such as surgery, radiotherapy or both, and systemic treatment with chemotherapy (chemotherapeutic drugs include alkylating agents, anthracyclines, antimetabolites, and antimicrotubule agents), hormone therapy (hormone treatments include aromatase inhibitors, antiestrogens, ovarian suppression, and ovarian ab-

lation), anti-HER2 therapy (including pertuzumab, trastuzumab), or a combination of all of them. Treatment choice is based on many factors: clinical and pathological aspects of the primary tumor, axillary lymph node status, expression of hormone receptors, HER2 overexpression, presence of metastasis, comorbidity, age and menopausal status.

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), a total of 115 clinical trials for breast cancer have been approved until 2018, half (65 clinical trials) of which were approved within the past ten years. These trials evaluate many drugs alone or in combination, such as: trastuzumab IV and SC, pertuzumab, capecitabine, trastuzumab emtansine, fulvestrant, anastrozole, sorafenib y olaparib.

It is necessary to mention the participation of Peru in the clinical trials that contributed in the approval of pertuzumab, a drug that with trastuzumab emtansine and chemotherapy with docetaxel has obtained a complete pathological response in 45.8% of the participants in a HER2 positive breast cancer in early stage. For this reason the FDA gave this medication an anticipate approval for this indication.



+ Prostate cancer

In 2017, prostate cancer was the second most common cancer after breast cancer in Peru. Prostate cancer is the most common cancer in men with a prevalence of 241 per 100,000 men. It is the third leading cancer-related cause of death and the most frequent cancer-related cause of death in men with 15 deaths per 100,000 men.

In recent years, the incidence of prostate cancer has increased in Peru, from 29 new cases per 100,000 men in 2010 to 35 new cases per 100,000 men in 2017. Prevalence has also increased in this period, from 193 per 100,000 men in 2010 to 241 per 100,000 men in 2017. The average age at diagnosis is around 65 years.

Prostate cancer incidence rate increases with age: from 80 new cases per 100,000 men aged 50-69 years, to 453 new cases per 100,000 men aged 70 years or older in 2017. Likewise, prostate cancer mortality increases with age: representing 2.33% of all deaths for men aged 50-69 years, and 5.17% of all deaths for men aged 70 years or older in 2017.

The slight increase in incidence and prevalence may be a result of improved surveillance, greater public awareness, and better screening. Since 2012, the guidelines for diagnosing prostate cancer in Peru recommend using the Prostate-Specific Antigen (PSA) test and/or digital rectal exam (DRE), followed by transrectal ultrasound (TRUS) and Transrectal Ultrasound-Guided Prostate Biopsy. However, the increase in prostate cancer incidence and prevalence may also be associated with obesity and the nutritional transition in Peru.

In Peru it is estimated that in 2017 alone, 693,366 healthy life years (HLY) were lost to cancer, of which, 36,482 HLYs were from prostate cancer, mainly due to premature mortality.

The overall 5-year survival rate of prostate cancer depends on the stage of diagnosis: at the localized stage, it can be up to 100%, if detected early, the 10- or 15-year survival rate can reach 98% and 95%, and at the final stages, the survival rate is 28%.

As described in the clinical practice guidelines in oncology, prostate cancer treatment choice is based on many factors, including cancer staging, risk of recurrence, life expectancy, as well as patient characteristics (age, comorbidity factors and personal preferences), and includes: active surveillance, surgery, radiation therapy, cryosurgery (if radiation therapy fails), hormone therapy (androgen suppressor therapy), sipuleucel-T Immunotherapy, chemotherapy (with docetaxel, cabazitaxel, mitoxantrone) and radiopharmaceuticals: radium-223, ^{89}Sr (strontium-89) and ^{153}Sm (samarium-153).

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 18 clinical trials for prostate cancer have been approved between 2000 and 2018. Of these, various treatment schemes were evaluated, either as single or combination therapies, including targeted vascular photodynamic therapy, nonsteroidal antiandrogens and tyrosine kinase inhibitors, among others.



+ Colorectal cancer

Between 2010 and 2017 colorectal cancer was the second most prevalent cancer in Peru, with 69 prevalent cases per 100,000 people in 2007. That same year, colorectal cancer was the third most common cancer in women, with a prevalence of 97 per 100,000 women, and the second most common cancer in men, with a prevalence of 42 per 100,000 men.

In 2017, the incidence of colorectal cancer was 13.8 new cases per 100,000 people. Women had a higher incidence than men: 17.6 new cases per 100,000 women compared to 10.1 new cases per 100,000 men. This same male to female incidence ratio is observed in age group 50-69: 41.6 new cases per 100,000 women compared to 27.6 new cases per 100,000 men. This ratio (2.9 to 1) is even more pronounced in ages 70 years or over: 185.29 new cases per 100,000 women compared to 97.5 new cases per 100,000 men.

In 2017, mortality from colorectal cancer represented 1.6% of total deaths, approximately 2,266 deaths.

Incidence increased as age increased: from 13.8 new cases per 100,000 people of all ages, to 34.7 new cases per 100,000 in people in age group 50-69, to 143 new cases per 100,000 in people aged 70 or over. The average age for colorectal cancer diagnosis was around 66 years.

In relation to rectal cancer, the Metropolitan Lima Cancer Registry reported 1,046 new cases of rectal cancer between 2010 and 2012, representing 1.7% of all malignant tumors and 53.1% of cases were in women. Rectal cancer was the 16th cause of cancer-related death in Metropolitan Lima, with a mortality rate of 1.6 deaths per 100,000 inhabitants.

In Peru about 46,947 healthy life years (HLY) were lost due to colorectal cancer, with a more noticeable effect in women, mainly due to late diagnosis and premature mortality in 2017.

In developed countries, early detection and timely treatment can increase the 5-year survival rate to just over 60% and the 10-year survival rate to 58%. When colorectal cancer is detected and treated early, the 5-year survival rate is 90%.



As described in the clinical practice guidelines in oncology, colon and rectal cancer treatment is based on many factors, including age, comorbidities, the patient's clinical status, the stage of cancer, cancer type. Treatment options include surgery, radiotherapy, chemotherapy (chemotherapeutic drugs include capecitabine, capecitabine plus oxaplatin, irinotecan, trifluridine plus tipiracil, floxuridine, fluorouracil, regimens with fluorouracil (5-FU) and leucovorin, oxaliplatin-based combinations (FOLFOX, FOLFOXIRI, FLOX), irinotecan-based combinations (FOLFIRI)); targeted therapy, which includes antiangiogenic therapy: bevacizumab, ramucirumab, regorafenib, ziv-aflibercept and epidermal growth factor receptor (EGFR) inhibitors: cetuximab, panitumumab, ablation, embolization as well as immunotherapy for rectal cancer (PD-1 and PD-L1 inhibitors: nivolumab, pembrolizumab).

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 9 clinical trials for colorectal cancer have been approved between 1999 and 2008. Of these, various treatment schemes were evaluated, as either single or combination therapies, with the vast majority of drugs being monoclonal antibodies and/or biological therapy (bevacizumab, capecitabine).

+ Gastric cancer

In Peru, as in the rest of the world, there has been an evident downward trend in gastric cancer incidence and age-standardized mortality rate from 2010 to 2017. This decrease may be due to public health initiatives that have addressed some underlying factors in certain types of gastric cancer, such as the treatment for *Helicobacter pylori*.

Despite this trend, gastric cancer is the second leading cause of death from cancer in the world, after lung cancer. The prognosis after diagnosis is generally poor and the rates of gastric cancer incidence and mortality are similar, being that it is one of the more aggressive cancers. In 2017, 13.07 new cases of gastric cancer per 100,000 inhabitants were reported in Peru, and gastric cancer deaths represented 3.07% of total deaths. For women, the gastric cancer incidence rate was reported at 27.96 new cases per 100,000 people in Peru in 2017, higher than in most countries in Europe and America.

In Peru, gastric cancer is the leading cause of death among cancers, as the main cause of death in women (3.09% of total deaths) and the second leading cause of death in men, with an estimated 5,000 deaths per year.

Gastric cancer risk increases with age. The incidence rate in age group 50-69 (32.53 per 100,000 people) is almost nine times higher than the incidence rate in age group 15-49 (3.62 per 100,000 people).

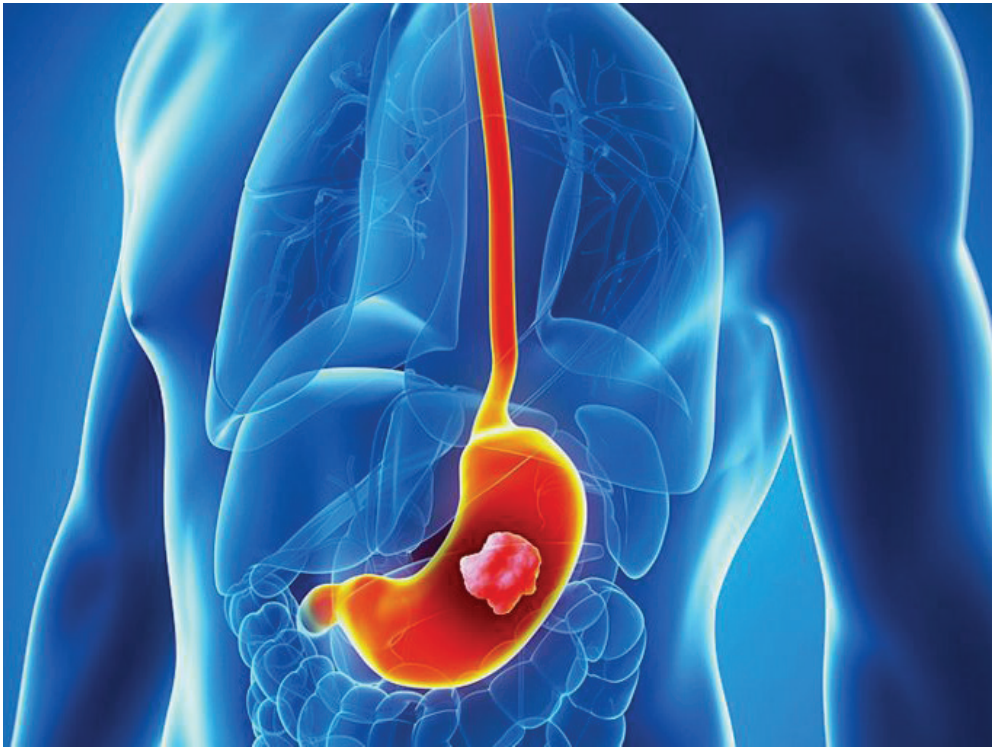
In age group 50-69 in Peru, the incidence rate in men is 32.53 new cases per 100,000 men while the incidence rate in women is 27.69 new cases per 100,000 women. In the general population, it is 14.34 new cases per 100,000 men versus 11.80 new cases per 100,000 women.

It is estimated that every year, 420,024 healthy life years (HLY) are lost to cancer, of which, 92,275 HLYs were from gastric cancer, mainly due to premature mortality.

As described in the clinical practice guidelines in oncology, gastric cancer treatment depends on many factors, including

the stage of cancer, clinical pathological characteristics and prognostic factors, and should involve a multidisciplinary care team in treatment planning. Treatment options include endoscopic treatment (endoscopic mucosal resection and endoscopic dissection of the submucosa), surgery, radiotherapy, chemotherapy (chemotherapeutic drugs include carboplatin, cisplatin, docetaxel, paclitaxel, capecitabine, epirubicin, fluorouracil or 5-FU, irinotecan, oxaliplatin) and targeted therapy (antiangiogenic therapy, ramucirumab, and anti-HER2 therapy using trastuzumab).

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 10 clinical trials have been approved between 2002 and 2018 in gastric cancer. Of these, various treatment schemes were evaluated, as either single or combination therapies, including monoclonal antibodies and biological therapy (capecitabine, trastuzumab IV).



+ Lung cancer

In Peru lung cancer is among the ten most common cancers.

In 2017 the prevalence rate of lung cancer was an estimated 9.1 cases per 100,000 people, with an incidence rate at 8.2 new cases per 100,000 people, representing 2.05% of the total deaths in the country.

Most patients with lung cancer are diagnosed in the final stages of the disease. The average age at diagnosis is about 70 years, because the disease is generally asymptomatic during the early stages. For that reason, only a very small percent (around 10-15%) is diagnosed at an early-localized stage. The five-year survival rate for local lung cancer is close to 55%, about 20% if it is limited to one region and less than 4% in the final stage. This explains why deaths related to lung cancer represents 2.05% of total deaths and prevalence and incidence rates are very similar.

Lung cancers are divided into two main histological groups: small cell lung carcinoma (SCLC) and non-SCLC (NSCLC). The second group is the more common. Cell type also influences survival rates, around 7% for SCLC and up to 21% for NSCLC.

In Peru, lung cancer (including trachea and bronchi cancer) was the tenth most frequent cancer in men and the twelfth in women in 2017. Lung cancer is the second leading cause of death among cancers (1.9% of total deaths), and the third leading cause of cancer-related death in men (2.11% of total deaths in men), while in women it is the second leading cause of death (1.97% of total deaths in women).

In Peru it is estimated that in 2017 alone, 693,366 healthy life years (HLY) were lost due to cancer, of which, 62,1000 HLYs were from lung, trachea and bronchi cancer, mainly due to premature mortality.

As described in the clinical practice guidelines in oncology, lung cancer treatment options depend on age, stage of cancer, as well as clinical pathological characteristics and prognostic factors. Treatments for NSCLC include surgery, radiotherapy, chemotherapy (chemotherapeutic drugs include carboplatin,



cisplatin, docetaxel, etoposide, gemcitabine, paclitaxel, pemetrexed, vinblastine sulfate, vinorelbine tartrate), and targeted therapy including epidermal growth factor receptor (EGFR) inhibitors: erlotinib, gefitinib, afatinib, osimertinib, cetuximab; anaplastic lymphoma kinase (ALK) inhibitors: crizotinib, ceritinib, alectinib, brigatinib; ROS1 inhibitors: crizotinib, ceritinib; BRAF V600E inhibitors: dabrafenib, trametinib; vascular endothelial growth factor (VEGF) inhibitors: bevacizumab, ramucirumab; and immunotherapy (PD-1 and PD-L1 inhibitors: atezolizumab, durvalumab, nivolumab, pembrolizumab)

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 46 clinical trials have been approved between 2003 and 2018, of which 44 are in NSCLC. Of these, various treatment schemes were evaluated, either as single or combination therapies, including monoclonal antibodies (atezolizumab, nivolumab, bevacizumab, pembrolizumab), immunotherapy, targeted therapy with ALK inhibitors (alectinib, crizotinib), and EGFR inhibitors (erlotinib), among others.

+ Acute lymphoblastic leukemia

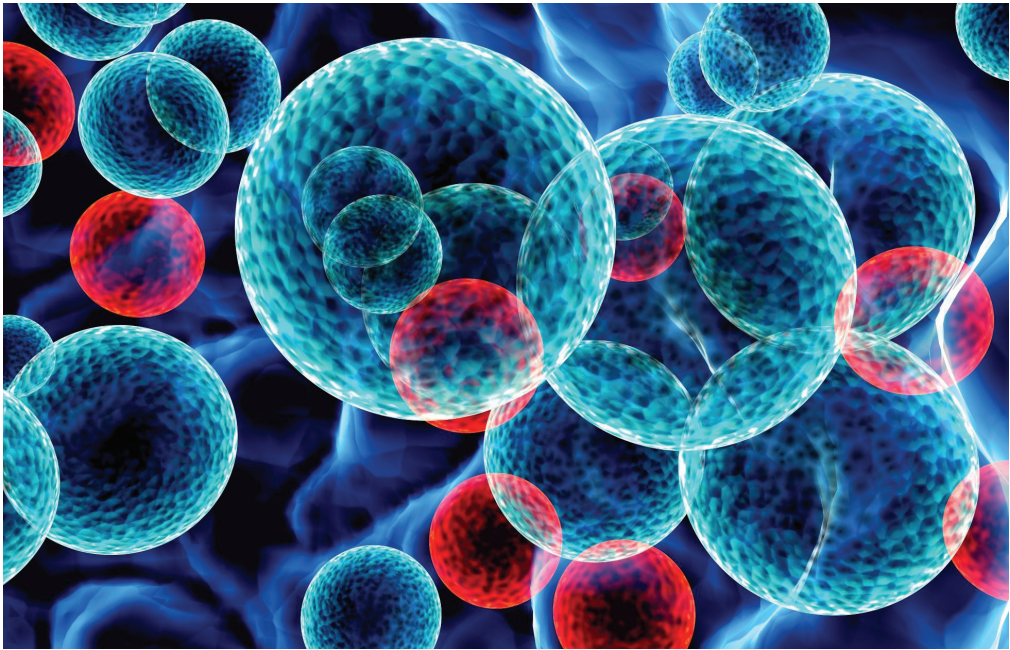
Leukemia is the most common childhood cancer from birth to age 14; however, most patients with leukemia are diagnosed at 20 years or older. There are four main types of leukemia according to affected hematopoietic stem cells and the time of illness: acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia. Acute lymphoblastic leukemia (ALL) is the most common type found in children, while other subtypes are more common in adults.

In 2017, the prevalence of ALL in the general population was 5.98 per 100,000 people, with 1.38 new cases per 100,000 people and representing 1.24% of total deaths in Peru. In 2017 the prevalence of ALL in children under 5 years was 17.3 per 100,000 children and 9.2 per 100,000 children aged 5 to 14 years. Blood cancer is considered a devastating disease because of its high mortality in children ages 5 to 14. In 2017 alone, ALL represented 4.13% of total deaths in this age group. On top of this, treatment costs are very expensive (chemotherapy and radiotherapy), and survival rate decreases as age at diagnosis increases.

It is estimated that in 2017 alone, 693,366 healthy life years (HLY) were lost to cancer, of which, 18,561 HLYs were from ALL, and more than half of these (9,797 HLY) were in children and adolescents under 15 years, affecting their quality of life and causing premature death, despite the fact that survival rates have increased in the last three decades, especially in children.

As described in the clinical practice guidelines in oncology, treatment choice for ALL is based on different factors such as age at diagnosis (children, adolescents, adults under 40, adults over 40) and the characteristics of leukemia cells (cellular subtypes, cytogenetic subtypes: Philadelphia chromosome). These factors can also affect and help predict the prognosis of the disease.

Treatment options include chemotherapy (chemotherapeutic drugs include alkylating agents, anthracyclines, antimetabolites,



sparaginasia erwinia chrysanthemi, cytarabine, nelarabine, pegaspargase, and vincristine, which is the standard treatment for ALL, with steroids being frequently administered together with chemotherapy drugs); targeted therapy (tyrosine kinase inhibitors: bosutinib, dasatinib, imatinib mesylate, nilotinib, ponatinib, used in the subtype of ALL with positive Philadelphia chromosome and monoclonal antibodies: rituximab, blinatumomab), stem cell transplantation (allogeneic stem cell transplantation is recommended for some patients with high-risk disease characteristics if a remission is not achieved or a recurrence occurred after remission induction chemotherapy), and radiation therapy.

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 29 clinical trials for leukemia have been approved between 2000 and 2018, the large majority in chronic myeloid leukemia (15 trials), followed by acute myeloid leukemia (4 trials) and leukemia acute lymphoblastic (3 trials). Of these, various treatment schemes were evaluated, either as single or combination therapies, including monoclonal antibodies (dasatinib, imatinib), and tyrosine kinase inhibitors, among others.

+ Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is heterogeneous group of neoplasms of the lymphoid system. There are more than 30 different types of NHL. Approximately 90% are B-cell lymphomas and 10% are T-cell lymphomas.

According to the National Institute of Neoplastic Diseases (INEN, acronym in Spanish), there has been an evident upward trend in the NHL incidence, and incidence rates are similar between men and women. The average age at diagnosis is 50 years, and its age range is quite large.

Diffuse large B-cell lymphoma (DLBCL) represents approximately 60-65% of B-cell lymphomas, according to the Cayetano Heredia and Arzobispo Loayza hospitals. The results reflect global epidemiological trends.

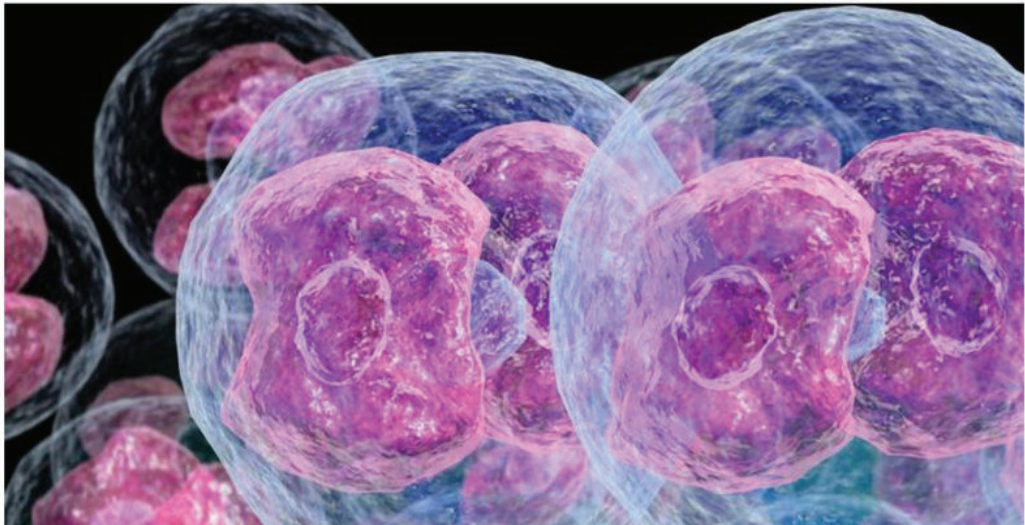
In 2017, lymphoma was the sixth leading cause of cancer death in men after prostate cancer, colorectal cancer, kidney cancer, leukemia and stomach cancer in Peru. In 2017 the prevalence of NHL was 10.23 per 100,000 people. There were 3.59 new cases per 100,000 people, and deaths from NHL represented 0.78% of all-cause mortality. In age group 50-69, the prevalence of NHL was 39.53 per 100,000 people, there were 10.94 new cases per 100,000 people, representing 1.24% of total deaths.

It is estimated that in 2017 alone, 693,366 healthy life years (HLY) were lost due to cancer, of which, 31,241HLYs were from lymphomas and myelomas, mainly due to premature mortality.

NHL can be divided into two groups, indolent and aggressive, each of which includes many subtypes according to how the disease progresses and responds to treatment. The type and stage of the lymphoma determines treatment and prognosis. The first course of treatment for all NHL subtypes is usually chemotherapy, either alone or in combination with radiation. Monoclonal antibodies are often administered with chemotherapy for B-cell lymphomas, and for some T-cell lymphomas.

As described in the clinical practice guidelines in oncology, DLBCL treatment options include immunotherapy (rituximab); immunomodulators (lenalidomide); chemotherapy (chemotherapeutic drugs include alkylating agents, anthracyclines, antimetabolites, etoposide, mitoxantrone); steroids (prednisone, methylprednisolone, dexamethasone); targeted therapy (brentuximab vedotin); radiotherapy, and transplantation of blood stem cells.

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), a total of 30 clinical trials for Non-Hodgkin Lymphomas have been approved between 2001 and 2018, the vast majority in B-cell lymphomas, the most frequent type being follicular lymphoma (8 trials) followed by DLBCL (6 trials). Of these, various treatment schemes were evaluated, either as single or combination therapies, including monoclonal antibodies (rituximab IV and SC), everolimus and biosimilars, among others.



+ Acute Coronary Syndrome

Cardiovascular disease (CVD) encompasses a range of human pathology. Acute Coronary Syndrome (ACS) is associated with sudden, reduced blood flow to the heart and is the leading cause of death in the world and a significant public health problem and major economic burden. Disease management is very costly and productivity loss is great.

In 2017 it represented one-third (31.8%) of all deaths worldwide. Ischemic heart disease (IHD) represented 16% of all deaths worldwide. More than three quarters of CVD deaths occur in low and middle-income countries.

In 2017, CVD-related deaths represented 19.6% of all deaths, and IHD-related deaths, 10.7% of all deaths in Peru.

In 2008 the Peruvian National Registry of Acute Myocardial Infarction reported cases of Acute Myocardial Infarction (MI) from 41 public and private hospitals, with the majority of patients in the coast (Lima, 71%), of which 65.2% had no previous history of coronary heart disease. Most (53.1%) were patients with ST-segment elevation myocardial infarction (STEMI), which were higher in younger men than in women, followed by NSTEMI (32.6%).

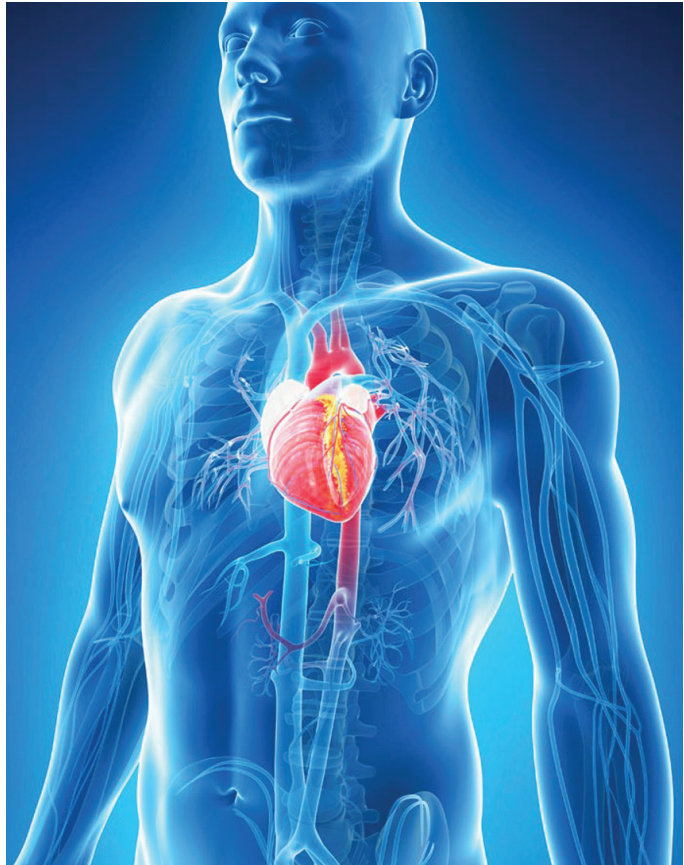
In 2017, the prevalence of IHD was 1,097 per 100,000 people, with an incidence of 70 new cases per 100,000 people. Prevalence was greater in the age group 50-69: 177 per 100,000 people.

In Peru it is estimated that in 2017, 569,748 healthy life years (HLY) were lost to IHD.

CVD can be prevented by adopting ideal cardiovascular health behaviors, including not smoking, healthy body mass index (BMI) ($<25 \text{ kg/m}^2$), regular physical exercise, eating healthy, total cholesterol level less than $<200 \text{ mg/dL}$, blood pressure at 120/80 mm Hg or lower, and fasting blood glucose at $<100 \text{ mg/dL}$. Since 2010, the American Heart Association (AHA) has defined CVD using these indicators and emphasized prevention, using this as a foundation for improving public health. Although

the CVD prevalence is low compared to other countries, when considering the indicators related to ideal cardiovascular health behaviors, only 1.3% successfully met 6 to 7 of the above criteria for effective CVD prevention in Peru in 2010.

If CVD health behaviors do not improve, CVD prevalence will increase in Peru. It is important to identify health strategies that address this, strengthening primary prevention of ACS and thus optimizing access to cost-effective interventions, increasing the quality and



accessibility of health care at different levels of the health care system. It is necessary to implement policies to generate national epidemiological data related to CVD, as well as to strengthen scientific research and adherence to Clinical Practice Guidelines.

The Clinical Practice Guidelines indicate that the management of the ACS, including diagnosis and treatment, begins at first medical contact. The electrocardiogram, particularly the presence or absence of ST-segment elevation, informs the immediate evaluation and triage of ACS patients. These tests are performed in a hospital with cardiac monitoring (MI with NSTEMI) or reperfusion therapy - PCI (percutaneous coronary intervention) or fibrinolysis, (STEMI) - and they must have the ability to continuously monitor and analyze cardiac rhythm and have quick access to a defibrillator.

Patients with STEMI should be treated immediately with primary PCI (reperfusion therapy of choice), and followed by angioplasty with a coronary stent. When primary PCI cannot be provided within 120 minutes of the ECG diagnosis, patients with STEMI should receive immediate thrombolytic therapy (pre-hospital or upon admission) with a fibrin-specific agent. Should this therapy fail, use rescue PCI and transfer to a PCI center. Successful thrombolytic therapy should be followed by early revascularization and coronary angiography.

Patients undergoing primary PCI should receive a combination of Dual Antiplatelet Therapy (DAPT) with aspirin and an ADP receptor blocker, as early as possible before angiography.

Patients who have recovered from a STEMI are at high risk for new events and premature death. Long-term interventions contemplate both lifestyle interventions and pharmacological treatments during and following hospital stay, which may include dual antiplatelet therapy, beta-blocker therapy, lipid-lowering therapy, calcium channel blockers, inhibitors of the angiotensin conversion enzyme and angiotensin receptor antagonists, in addition to early psychosocial interventions, among others.

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 20 clinical trials for ACS have been approved between 1999 and 2008. Of these, various treatment schemes were evaluated, either as single or combination therapies, including: dual antiplatelet therapy as ticagrelor, therapy anticoagulant and thrombolytic therapy as tenecteplase, and the combination of ezetimibine/simvastatin for the prevention of coronary syndromes. In addition, many clinical trials to determine possible cardiovascular repercussions of the treatment of other diseases (outcomes studies) have been performed in the country.

+ Diabetes Mellitus

In recent decades, diabetes mellitus has become a main public health problem worldwide, a result of major lifestyle changes caused by poor dietary habits, an increase in sedentary behavior and a reduction in physical activity, which are associated with economic transition, urbanization, globalization and industrialization. In Peru, youth are at risk for developing diabetes at a younger age while detection still occurs during the later stages, resulting in greater complications.

In 2017, the incidence of diabetes in Peru was 198 new cases per 100,000 people, and 424 new cases per 100,000 people in age group 50-59, the highest incidence of all age groups. The International Diabetes Federation estimated that in 2017 in Peru there were 1,308,000 people living with the disease, of which 40% were between 20 and 79 years and not diagnosed. Diabetes-related mortality among people under 60 years is around 62.2%.

In Peru, it is estimated that in 2017, 339,792 healthy life years (HLY) were lost to diabetes and kidney disease, of which, 206,474 HLYs were from diabetes mellitus.

Despite the efforts made in Peru and other developing countries to curb the disease, it is challenging to increase access to health care and improve follow-up in the long term, requiring appropriate diagnostic tests, effective medications, and treatment and management strategies for diabetes complications and comorbidities. In general, better health management is needed to respond to these challenges.

The American Diabetes Association (ADA) outlined in its 2018 Standards of Medical Care in Diabetes, the importance of using both non-pharmacological (including self-management education, nutrition, physical activity, among others) and pharmacological interventions.

Pharmacological treatment of T2DM should be initiated using biguanide class drugs when glycosylated hemoglobin (HbA1c) is $<9\%$, while insulin therapy should be initiated (alone or in association) in markedly symptomatic patients, patients newly diagnosed with HbA1c $\geq 10\%$ or patients with TG ≥ 300 mg/dL.



In patients without atherosclerotic cardiovascular disease (ACVD), if monotherapy fails to achieve target HbA1c levels in 3 months, add an additional antihyperglycemic agent (sulfonylureas, thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, basal insulin, sodium-glucose transporter type 2 inhibitors or SGLT2) based on drug-specific and patient factors. In patients with ACVD, it is recommended to add an agent proven to reduce major adverse cardiovascular events and mortality (SGLT2 inhibitors, GLP-1 receptor agonists) after considering drug-specific and patient factors.

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 144 clinical trials for diabetes mellitus have been approved to date, and since 2008, 67 clinical trials in type 2 diabetes mellitus. In the last five years, various treatment schemes were evaluated such as: GLP-1 receptor agonists (albiglutide and lixisenatide), long-acting insulin analogs, dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptine, vildagliptine and saxagliptine), sodium transporter inhibitors-type 2 glucose (SGLT2) (dapaglifozine, canaglifozine and empaglifozine) and new types of insulin like U300.

+ Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterized by persistent respiratory symptoms and limited airflow due to respiratory abnormalities caused by exposure to harmful particles or gases. Since 2015 it has been the third leading cause of death worldwide and the seventh leading cause of death in Peru. The global burden of COPD is predicted to increase in the coming decades due to continued exposure to risk factors for COPD and population aging.

Prevalence data may vary given that many epidemiological studies do not diagnose COPD using spirometry. In Latin America, the Latin-American Pulmonary Obstruction Investigation Project (PLATINO, acronym in Portuguese) and Prevalence of COPD in Colombia (PREPOCOL, acronym in Spanish) studies, determined that COPD was an important contributor to global burden of disease - its prevalence ranging from 8% to 20% - and identified COPD risk factors and factors related to its low diagnosis.

In 2017, Peru had an estimated prevalence of 2,115 per 100,000 people. In the last two decades, prevalence has increased particularly in women, from 1,913 per 100,000 women in 2007 to 2,072 per 100,000 women in 2017. COPD is a major cause of chronic morbidity and mortality and constitutes a substantial public health challenge. In Peru, COPD represented for 5.28% of all deaths in 2017, its incidence increasing with age: 137 per 100,000 people in the general population, 303 per 100,000 people aged 50-69, and 945 per 100,000 people aged 70 or older.

Although smoking is the leading cause of COPD, there are other risk factors, including genetic factors, long-term asthma, tuberculosis, outdoor air pollution, exposure to secondhand smoke and biomass fuels, and work-related exposure, among others. In Peru, risk factor exposure depends on geographical context; rural areas experience greater exposure to biomass fuels while in urban areas prevalence varies due to smoking and history of respiratory diseases, including post treatment of tuberculosis and asthma.



In Peru, it is estimated that in 2017 alone, 249,229 healthy life years (HLY) were lost to chronic respiratory illness, of which, 91,649 HLYs were from COPD, which is among the top 50 conditions with the greatest disease burden, and merits further study.

The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) published guidelines for the diagnosis, management and prevention of COPD, in which it describes the importance of both non-pharmacological measures (self-management education, vaccinations, nutrition, physical activity, among others) and pharmacological measures, highlighting that each treatment regimen should be individualized and should be

based on the severity of the symptoms, risk of exacerbations, side effects, comorbidities, availability and cost of medication and patient response, as well as preference and the ability to use various medication administration devices.

Treatment options include the following: 1) Pharmacotherapy for smoking cessation; 2) Short-acting and long-acting bronchodilators, anti-inflammatory drugs; 3) Antibiotics: long-term treatment with azithromycin and erythromycin for the reduction of exacerbations; 4) Mucolytics/antioxidants; 5) Pulmonary rehabilitation; 6) Oxygen therapy and respiratory support; and 7) Interventional treatment: surgery to reduce lung volume, bullectomy, transplant.

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 33 clinical trials for COPD have been approved between 1999 and 2018. Of these, various treatment schemes were evaluated, as either single or combination therapies, including monoclonal antibody therapy and bronchodilator therapy.

Asthma is one of the most common noncommunicable diseases, and is becoming more frequent among children. Asthma has a large economic burden on healthcare systems and society: asthma reduces labor productivity and, childhood asthma's high morbidity impacts school attendance and performance, and family life.

Peru has one of the highest prevalences in the world. The ISAAC study (International Study of Asthma and Allergies in Childhood), conducted in 2003, reported that Lima has one of the highest prevalences of asthma in children (19.6%) among the cities of more than 50 countries. The prevalence of asthma in Peru in 2017 was 10,784 per 100,000 children under 5 years and 10,361 per 100,000 children in age group 5-14. The incidence in children was 5,877 new cases per 100,000 children under 5 years.

An increased risk of asthma is associated with the presence of indoor and outdoor air pollutants and allergens, residence in urban areas, respiratory infections, exercise, smoking, irritating toxic substances, diet, genetics and body mass index. The Peru Urban versus Rural Asthma (PURA) study, conducted in adolescents between ages 13 and 15, identified risk factors for asthma, including degrees of urbanization. The study found that in general, asthma rates are higher in urban areas. However, *severe persistent* asthma in adolescents which more prevalent in rural areas than in urban areas: 14% in Tumbes vs. 5% in Lima.

Asthma-related mortality is higher in developing countries. In Peru, asthma-related deaths in children under 5 years of age has decreased: 0.068% of all deaths in 2008 to 0.037% in 2017.

In Peru, it is estimated that in 2017 alone, 240,229 healthy life years (HLY) were lost to chronic respiratory diseases, of which, 71,504HLYs were due to asthma.

The 2018 Global Initiative for Asthma (GINA) report, based on the Global Strategy for the Management and Prevention of Asthma, describes the importance of a stepwise approach to treatment, tailored to the individual patient. Treatment options for asthma

includes medication, treating modifiable risk factors, non-pharmacological interventions, and guided asthma self-management education and skills training.

Treatment involves a continuous cycle involving assessment, treatment and review. Asthma medications include:

Control medications: Inhaled corticosteroids (ICS), combinations of ICS and long-acting β 2-agonists (LABA), leukotrienes modifiers (tablets), chromones (pMDI or DPI).



Control medications: Add-on therapies: Long-acting anticholinergics: tiotropium., anti Immunoglobulin E (Anti-IgE) therapy, anti interleukin-5 (Anti-IL5): mepolizumab or benralizumab SC (≥ 12 years old); Intravenous (IV) Reslizumab (≥ 18 years old) and systemic corticosteroids.

Symptomatic medications: Short-acting inhaled β 2-agonists (SABA) (pMDI, DPI), low doses of ICS / formoterol, short-acting anticholinergics (pMDI or DPI), for example, ipratropium bromide and oxitropium bromide.

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 46 clinical trials for asthma have been approved between 2008 and 2018. Of these, various treatment schemes were evaluated, either as single or combination therapies (budesonida/formoterol), including bronchodilator and monoclonal antibody therapies (reslizumab, omalizumab, benralizumab).

+ Rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most common causes of disability in adults, particularly those with multiple chronic diseases. RA has a worldwide reach and its prevalence ranges from 0.1% to 0.6% depending on geographical area. In Peru, its prevalence is 0.5%, according to the *WHO-ILAR Community Oriented Program for Control of Rheumatic Diseases (COPCORD)* study, published in 2009 and conducted in a marginalized urban area in Lima.

In Peru, much like other Latin American countries, the age of onset of RA is 40, 10 years younger than in some developed countries. In 2017, the prevalence was 271 per 100,000 people. The female to male prevalence ratio is over 2 to 1: 385 per 100,000 women compared to 160 per 100,000 men. The female to male incidence ratio is similar in age group 15-49: 24 new cases per 100,000 women compared to 10 new cases per 100,000 men.

In Peru, it is estimated that in 2017 about 492,309 healthy life years (HLY) were lost due to osteomuscular and connective tissue related conditions, of which 13,319 HLYs were from RA, which is among the top 50 conditions with the greatest disease burden, and merits further study.

In Peru, RA-related mortality has tended to decrease. For 2017, it is 0.3 deaths per 100,000 in 2010, and 0.22 deaths per 100,000. However, since RA is a systemic, progressive and chronic disease, it has an important impact in patients' quality of life, requiring early detection, optimal pharmaceutical management, and treatment of complications and comorbidities in order to slow RA's advance and improve quality of life.

The "treat to target" strategy aims to coax the disease into remission or low activity. This treatment option uses both non-pharmaceutical (self-management education, nutrition, among others) and pharmaceutical interventions.

The 2018 International Clinical Practice Guidelines recommend the following treatment protocols:

First line of treatment includes monotherapy with disease-modifying antirheumatic drugs (DMARDs): oral methotrexate, leflunomide or sulfasalazine.

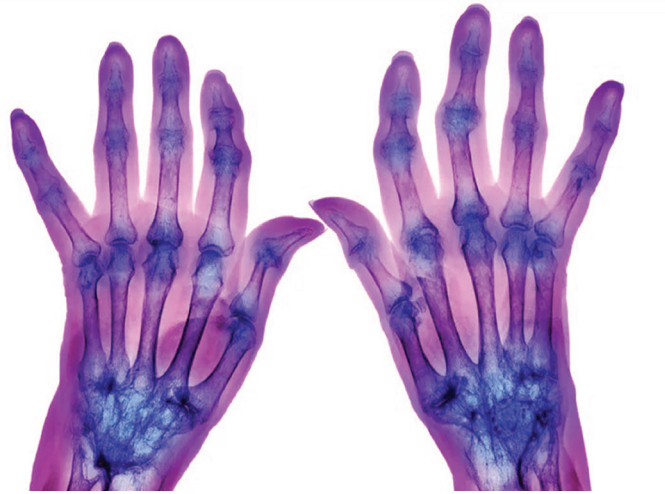
If the disease is not properly managed, the guidelines recommend adding another DMARD

agent to monotherapy (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine). One may also use glucocorticoids (oral, intramuscular or intra-articular) as an interim treatment or “bridge therapy” in the short term.

If the patient responds to the conventional DMARD therapy, they may continue with biological therapy: sarilumab, adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab y abatacept, either as a single therapy or in combination with methotrexate.

For severe rheumatoid arthritis, immunomodulatory therapies (baricitinib and tofacitinib) each in combination with methotrexate, can be effective treatment options for patients who have had an inadequate response to other DMARDs.

According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 43 clinical trials for RA have been approved between 2008 and 2018, most of them included biologic therapy (tocilizumab, rituximab IV, golimumab, abatacept, tofacitinib) in different schemes alone or in combination.



+ Alzheimer's disease

Dementia, including Alzheimer's disease, is a major public health issue. It currently affects more than 35 million people worldwide, a figure that will double by 2030 and triple by 2050, affecting 115 million people. According to the Pan American Health Organization (PAHO), the Americas has gained more than 20 years in life expectancy during the last half century alone. By 2020, it will have 200 million older people, and more than half of them will live in Latin America and the Caribbean. It is estimated that by 2050 16 million people with dementia will live in Latin America and the Caribbean compared to 11 million people in North America. From 2010 to 2050, the number of people living with dementia will increase by 445% in the Andean region. By 2050, an estimated 748,000 people will live with dementia in Peru.

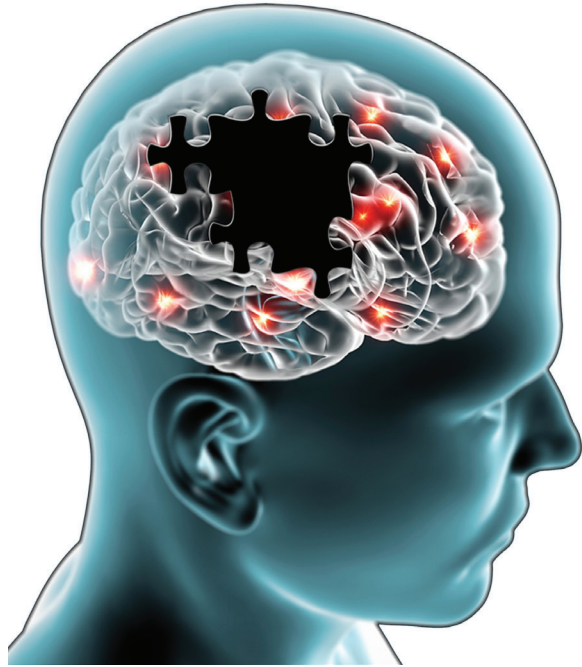
Compared to their European counterparts, Latin America shows higher rates of dementia for both genders in age group 65-69, and for women in age group 70-74.

In Peru it is estimated that in 2017 alone, 514,118 healthy life years (HLY) were lost to neuropsychiatric diseases, of which, 45,472 HLYs were from dementia, becoming the leading burden of disease (by disease category), mainly due to morbidity.

In 2017, Peru had an estimated prevalence of 501 per 100,000 people, and incidence of 82 new cases per 100,000 people for Alzheimer's disease and other dementias. Prevalence was higher people aged 70 years or older - 8,369 per 100,000 people - representing 12.65% of all deaths and a loss of 99,915 HLY for that age group.

Alzheimer's disease treatment and management should look to an individualized approach, and consider the patient's symptoms and social support structure. The first step after diagnosis is supportive treatment that is, providing education, support and resources to both the patient and the family. This includes:

- Treatment for cognitive impairment: cholinesterase inhibitors and N-methyl-D-aspartate (DMDA) receptor antagonists.
- Management of behavioral and psychological symptoms using non-pharmacological and pharmacological interventions: selective serotonin-noradrenaline (norepinephrine) reuptake inhibitors. Short-acting oral/intramuscular benzodiazepines or mood stabilizers, such as carbamazepine, should be considered when alternative strategies and repeated confirmation (reassurance) have failed.
- Insomnia management: treatment of first choice, sleep hygiene; second choice, trazodone.
- In the case of severe illness or when cholinesterase inhibitors are not tolerated or ineffective, memantine is recommended for those with moderate to severe dementia. It can be used alone or together with cholinesterase inhibitors in severe dementia.



According to the Peruvian Registry of Clinical Trials (REPEC, acronym in Spanish), 9 clinical trials for Alzheimer's have been approved between 2003 and 2018. Of these, various treatment schemes were evaluated, either as single or combination therapies, including cholinesterase inhibitors, inhibitors of the secretase and monoclonal antibodies, among others.

The development in clinical trials in Peru has allowed community awareness about necessity and relevance of this kind of research. However, we still need to promote the importance of health research and the clinical trials as a source of scientific knowledge in order to improve the country's decision-making process in health conditions. The brief epidemiologic information recollected in this document shows that the need is present. Peru has the regulatory, sanitary, epidemiologic, professional and facilities conditions to develop world class clinical research; these characteristics added to our diversity from the genetic and cultural point of view, generate interesting opportunities to make us a regional reference in the development of clinical trials. Finally, besides promoting the development of all the stakeholders of this activity in the country, clinical trials also give scientific evidence of new treatments for our population.

(Note)

This document is the first part of a series we expect to update periodically and to extend it with more epidemiologic information about new pathologies. The information of more pathologies, as the bibliography in which it this document was based can be found in the following link:

<http://alafarpe.org.pe/>



Machu Picchu located in Cusco, Peru; World Heritage according to UNESCO and one of the new 7 wonders of the modern world according to NOWC.



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