euroespes health

Vol. 17 / October 2021

EuroEspes Health Medical Bulletin

International Center of Neuroscience
and Genomic Medicine

Contents

October Editorial
Mental Health Murkiness

The noble intentions of the Declaration of Almá-Atá have remained in the nostalgic memory of the romantics who gave birth to them. Perhaps the most remarkable points about that meeting, organized in Kazakhstan from September 6 to 12, 1978, by the World Health Organization (WHO), the Pan American Health Organization (PAHO) and UNICEF, sponsored by the former USSR, were its first two statements: (I) Health is a state of complete physical, mental and social well-being, and not only the absence of affections or diseases; it is a fundamental human right; achieving the highest attainable standard of health is an extremely important social goal throughout the world, the realization of which requires the involvement of many other social and economic sectors in addition to the health one. (II) The serious inequality that prevails in the current health status of the population, especially between developing and developed countries, as well as within each country, is politically, socially, and economically unacceptable and, therefore, a matter of common concern for all countries.

This conceptually impeccable declaration has been negligently ignored by the entire world, calling into question - once again - the little value of the grandiloquent declarations of international organizations whose credibility and specific weight in the decisions of the States is more than questionable. Since then, the Berlin Wall has fallen on November 8, 1989; many American presidents have passed through the White House (**Jimmy Carter**, 1977-1981; **Ronald Reagan**, 1981-1989; **George HW Bush**, 1989-1993; **Bill Clinton**, 1993-2001; **George W. Bush**, 2001-2009; **Barack Obama**, 2009-2017; **Donald Trump**, 2017-2021; **Joe Biden**, 2021-); the European Economic Community (EEC), created by the 1957 Treaty of Rome, joined the European Union in 1993 and was renamed the European Community (EC), only to disappear in 2009 in the institutional framework of the European Union; many failed states gave up in Africa; unfortunately, several banana republics were born, vanished and revived in Ibero-America; Castro orphaned Cuba; and Japan ceded Asian hegemony to China.

In the field of medical sciences, among many relevant events, the works of **Frederick Sanger** in genomics stand out; the invention of PCR by **Kary Mullis** in 1983; the appearance of AIDS in 1981 and the discovery of HIV by **Luc Montagnier** in 1983, recipient of the Nobel Prize in Medicine, together with **Françoise Barré-Sinoussi** and **Harald zur Hausen** in 2008; the cloning of Dolly in 1996; the presentation of the first draft of the Human Genome in February 2001, thanks to the public and private consortia led by **Francis Collins** and **Craig Venter**, respectively; the subsequent sequencing of the genome of various species; and the gradual consolidation of genomic medicine and pharmacogenetics, postulated by **Motulsky** in 1957, **Frederich Vogel** in 1959, and **Kallow** in 1962. The explosive evolution of epigenetics was also relevant, introduced by **Conrad Waddington** in 1942, to explain the mechanisms that regulate gene expression and the dialogue of the genome with the environment. Among the epidemiological disasters, Ebola, a disease caused by 5 species of viruses, had to be dealt with: Bundibugyo ebolavirus (BDBV), Reston ebolavirus (RESTV), Sudan ebolavirus (SUDV), Taï Forest ebolavirus (TAFV) and Zaire ebolavirus (ZEBOV) ; Zika virus, from the family of dengue, yellow fever, Japanese encephalitis and West Nile virus, which since the 1950s moved within the equatorial belt from Africa to Asia, but which from 2007 to 2016 spread to the East, across the Pacific Ocean to the Americas, and led to the 2015-2016 epidemic; and, above all, to the catastrophe of the COVID-19 pandemic due to coronavirus that called into question the solvency of the health systems of all developed countries.

In parallel, there have been important discoveries in the field of neurosciences, from **Gerald Edelman** 's theory of neural Darwinism in 1978 to the American *Human Connectome Project* to map the human brain in 2009 or the *Human Brain Projec*t of the European Union to simulate brain functions by computer in 2013. In the field of psychopharmacology, there were also important advances related to neurohormones, alcohol, antidepressants, antipsychotics, benzodiazepines, hallucinogens, hypnotics, sedatives, opiates, cannabis and stimulants. Intensive work was carried out on understanding neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis and multiple sclerosis. However, the epidemiology and the socio-sanitary and economic impact of the three great killers that murder Western society (cardiovascular diseases, cancer, brain disorders) were not altered or even magnified. In the case of mental illness, it is estimated that over 450 million people suffer from a mental disorder, among which are anxiety (from 2.4% to 18.2% of the population), depression (1-10%), drug addiction (0.1-7%), and impulse control disorders (0.1-6.8%). In terms of morbidity and mortality, brain disorders represent 10-15%, but the prevalence of episodes of mental impairment throughout life could reach 65-85% of the population with different degrees of severity (mild, 1.8-10%; moderate, 0.5-9.4%; severe, 0.4-7.7%). In the United States, almost half of the population meet criteria for a mental disorder: anxiety (28.8%), depression (20.8%), impulse control disorder (24.8%), substance abuse (14.6%). In Europe, it is calculated that mental disorders - which in global figures do not differ from the American statistics - are mild in 22.3% of cases, moderate in 37.3% and serious in 40.4%. It is disturbing that 50% of these cases appear during adolescence and 75% around 34 years of age.

Many of these figures may be inflated, due to the rigidity of orthodox criteria plagued with misconceptions that demand revision. Overdiagnosis of mental problems stigmatizes the family and the society. Neither a child angered by family disruption or school inattention can be branded with a paidopsychiatric diagnosis; nor an individual suffering from dementia who is ignored or irritated with inappropriate behaviors (abandonment, contempt, ridicule) by his caregivers, should be hung the stigma of conduct disorder on him, with the consequent taking of unnecessary psychotropic drugs to calm him down. A child with school difficulties should not be marked with the stigma of school failurewithout first examining whether his brain is the victim of previous organic problems (dystocic deliveries, abuse of caesarean sections, perinatal microinjuries, anemia, poor diet, severe dysbiosis) or if his problems result from the socio-family environment in which he lives.

The opposite is also possible. The official medical orthodoxy understands that there is disease when there are symptoms; which is clearly uncertain. One may have no symptoms and be dying (a blocked coronary artery that causes a fulminant myocardial infarction; a silent cancer that kills us in weeks; a sudden stroke without prodromes). All neurodegenerative diseases are asymptomatic for decades and when they show symptoms, our brain is already so damaged that repair is impossible. We can be seriously ill without knowing it. The existence of disease does not require subjective symptoms. In the youth environment, ignorance or the occult means that users of alcohol, cannabis, cocaine or opiates do not show apparent symptoms while their brains are de-sprouted and their neurons dry up like when we throw bleach on the grass in the garden.

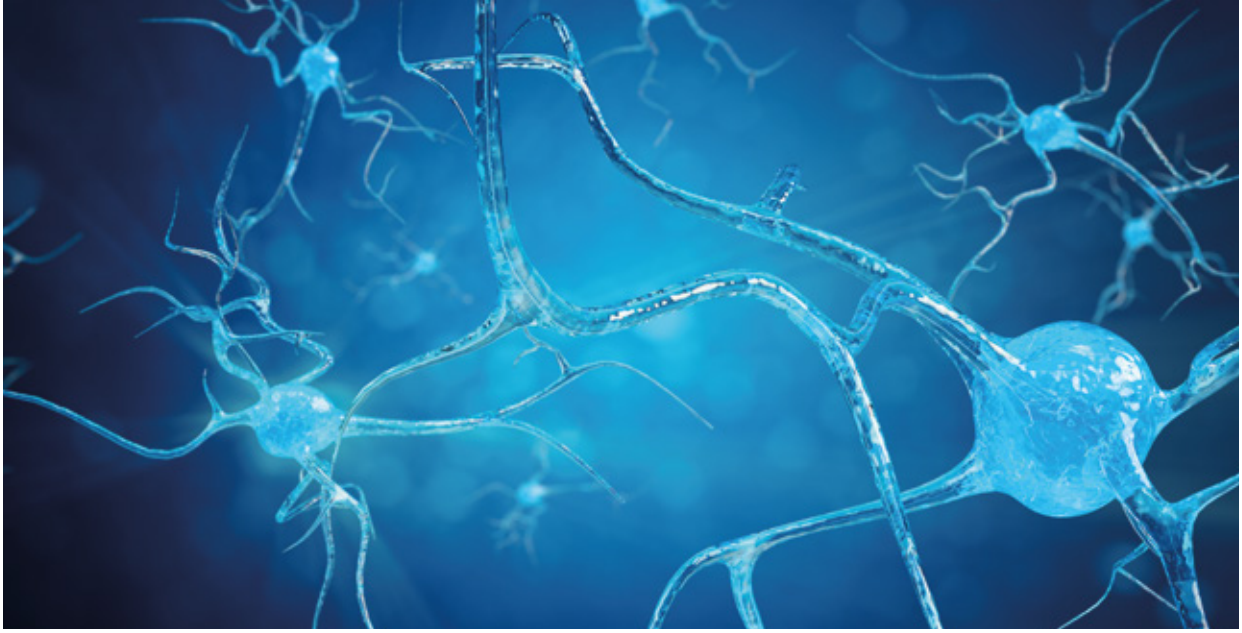
The inappropriate use of drugs is becoming a serious health problem, with more than 15% of hospitalizations in those over 50 years of age. In the adult population and in the elderly, for problems that require chronic treatments, the misuse of drugs causes multiple mental disorders. The typical case is the parkinsonian patient who is treated with excessive doses of L-DOPA or dopaminergic agents and ends up developing a case of agitation or a psychotic disorder; this patient is then administered a neuroleptic to correct his mental condition, which aggravates his movement disorder; or the patient with dementia who inappropriately receives benzodiazepines or antipsychotics to stay calm, thereby accelerating memory impairment and functional disability.

The pharmacological management of the brain is a complex task that requires extensive experience in the use of psychotropic drugs in order not to harm patients. More than 60% of patients receive wrong or harmful treatments when the prescriber does not know their pharmacogenetic profile. Just as cancer, dementia, or heart disease can now be predicted with genomic markers, the pharmacological response can also be predicted by knowing the pharmacogenetic profile of each patient.

Science provides us with the appropriate tools to optimize diagnoses and treatments. Almost no procedure in medicine is perfect or 100% infallible, but almost all are better than the primitivism of ignorant attitudes. The global access to knowledge that the general population has today and individual responsibility for the benefit of their own and collective health forces us not to ignore the new forms of medical action that scientific progress gives us. It is the responsibility of the doctor to use them correctly and it is the responsibility of the patient to comply with the guidelines that health professionals recommend.

More than 40% of medical treatment failures are due to therapeutic non-compliance. When it comes to mental health, we are playing with our dignity; and dignity does not admit games of chance or folkloric experiments with unforeseeable consequences. The brain always warns and never forgives.

Ramón Cacabelos
Professor of Genomic Medicine



EuroEspes announces a new epinutraceutical bioproduct for the prevention of Alzheimer's disease

The EuroEspes Management Committee, chaired by Dr. Ramón Cacabelos, which includes Mr. Javier Loizaga, president of Moira, main shareholder of EuroEspes, Mr. Pedro Fuente, vice president, Mr. Javier Elosúa, member of the Board, Mr. Jaime Pombo, general director, and Mr. Francisco Álvarez, financial director, announces the introduction of a new epinutraceutical bioproduct for the prevention and treatment of Alzheimer's disease. This new biopharmaceutical agent has been developed entirely by EuroEspes scientists, under the direction of Dr. Cacabelos, with the participation of Dr. Iván Carrera, Head of the Department of Health Biotechnology, Dr. Olaia Martínez, Head of the Department of Medical Epigenetics, Dr. Vinogran Naidoo, Head of the Department of Basic Neurosciences, Dr. Lola Corzo, Head of the Department of Medical Biochemistry, and the industrial production team led by José Manuel Rodríguez at EuroEspes Biotecnología (Ebiotec).

The new product is in the patent registration process and will be commercialized next year under the name *BrainRex*. It is the fourth product in a line of research of new products for diseases of the nervous system. The first was the EB-101 vaccine against Alzheimer's disease, approved by the United States Patent Office; the second, Atremorine, for the prevention and treatment of Parkinson's disease, approved by the European patent office; the third, NeoBrainine, a hybrid of citicoline, pantothenic acid and niacin with neuroprotective properties for neurodegenerative and cerebrovascular diseases; and the fourth, BrainRex, a product belonging to the animal biotechnology line, extracted from the brain of artiodactyl mammals of the Suidae family, to which the pig and wild boar belong.

In transgenic animals, in whose murine genome the genes responsible for Alzheimer's disease have been inserted, BrainRex prevents the development of the disease with an efficiency greater than 80% when administered prophylactically. Administered in early periods, it delays the neurodegenerative process with an efficiency of 60%. In addition to being a powerful neuroprotective agent, which increases neuronal survival and inhibits the formation of β-amyloid protein deposits, BrainRex has a powerful anti-neuroinflammatory effect; but, above all, its powerful epigenetic effect stands out, regulating the expression of abnormal genes associated with the etiopathogenesis of Alzheimer's disease, hence its characterization as an epinutraceutical bioproduct; the first in a range of epinutraceutical agents developed in the laboratories of the International Center for Neuroscience and Genomic Medicine. As an epinutraceutical agent, BrainRex reverses the global hypomethylation of DNA exhibited by

Alzheimer's patients and behaves as a powerful enhancer of DNMT3a (*DNA Methyltransferase 3a*), modulator of Sirtuin-1 and inhibitor of HDAC (*Histone deacetylase*). These properties give it a unique and exclusive character. No other similar product is available on the market at the moment.

Scientists from EuroEspes discover that Alzheimer's disease patients accumulate a large number of defective genes in their genome

An extensive study, carried out at the International Center of Neuroscience and Genomic Medicine, under the direction of Dr. Ramón Cacabelos, shows that patients with Alzheimer's disease (AD) accumulate a large number of defective genes in their genome. The work will be published in the third edition of a special volume of *Methods in Molecular Biology* (Springer), entitled *Pharmacogenomics in Drug Discovery and Development* and edited by Dr. Qing Yan, from Santa Clara, California, USA.

The work is the result of the multidisciplinary effort of several departments: Genomics and Pharmacogenomics (Dr. Juan Carlos Carril), Neurosciences (Dr. Vinogran Naidoo), Medical Epigenetics (Dra. Olaia Martínez-Iglesias), Medical Biochemistry (Lola Corzo), Scientific Documentation (Natalia Cacabelos) and Neuropsychology (Rocío Pego), as well as the nursing, neuroimaging, digital diagnosis and satellite specialties teams.

In the last 30 years, more than 600 genes distributed throughout the human genome have been linked to the risk of AD. Several pathogenic mutations in the genes of the β-amyloid protein precursor (APP) (mutations> 50), presenilin 1 (PSEN1) (mutations> 300) and presenilin 2 (PSEN2) (mutations> 40), present in less than 10% of the cases, confer to AD the condition of a cerebral amyloidopathy. Mutations in the tau gene (MAPT) (> 100 mutations are associated with various tauopathies: frontotemporal dementia, Pick's disease) link AD with other tauopathies, although MAPT variants are not specific to the prototypical forms of AD. Amyloidopathy and tauopathy have been the two dominant hypotheses in the etiopathogenesis of AD for years.

Nonsense APP mutations in early AD cause familial AD, while the coding variant APP-A673T reduces the risk of AD. Mutations associated with the risk of AD in the APP gene increase total Aβ levels, Aβ42 levels, or Aβ fibrillogenesis, while protective alleles reduce Aβ levels.

Presenilin is the catalytic site of γ-secretase and the most dominant mutations associated with familial AD occur in the APP gene that encodes the substrate of the amyloid precursor protein, or in the PSEN1 and PSEN2 genes that encode the responsible protease (presenilin) of APP cleavage, leading to abnormal accumulation and deposition of Aβ in senile plaques and blood vessels. Apolipoprotein E4 (APOE-4), the most important risk factor for AD in>

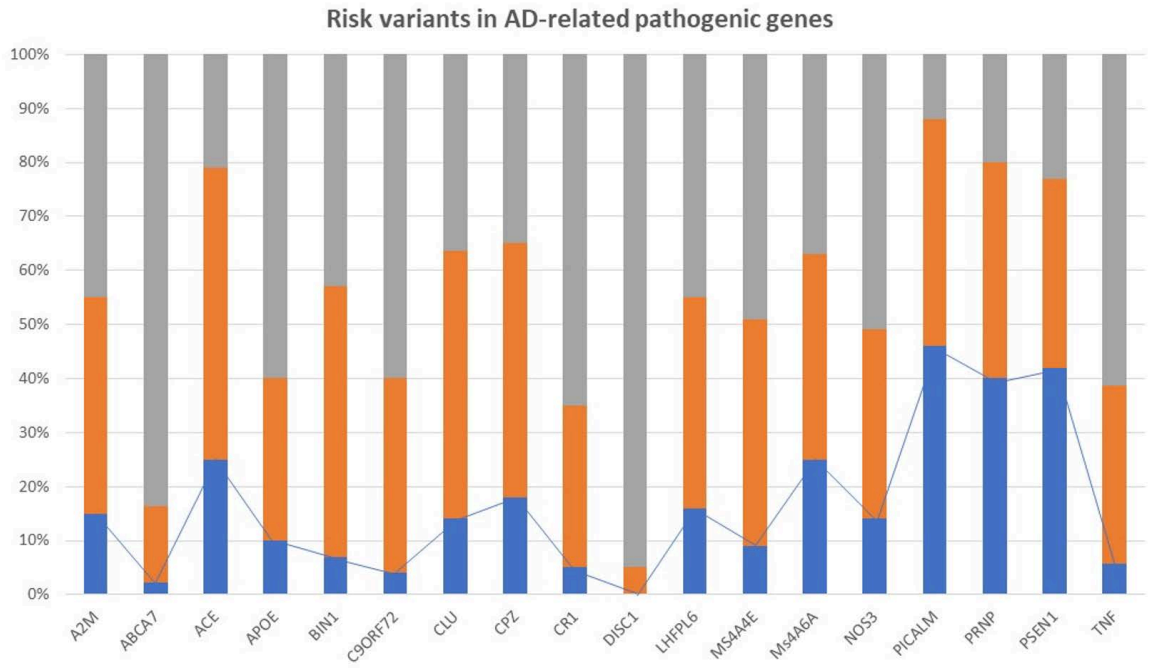
40% of cases, affects the clearance of Aβ from brain tissue. Immunotherapy with different A β antibodies (solanezumab, crenezumab, and aducanumab) attempts to reduce Aβ and slow down cognitive decline in presymptomatic and / or mild cases of AD, as a new line of therapeutic intervention.

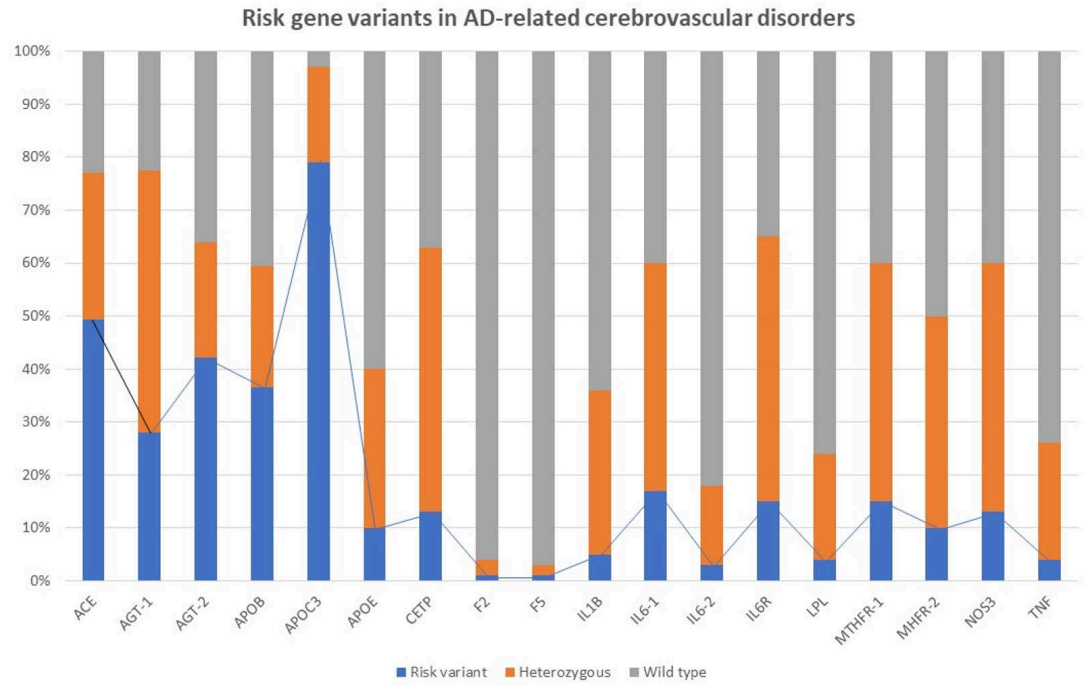
In addition to these pathogenic genes, many other genes, as well as new mutations in PSEN1, have been identified in association with AD in recent genomic sequencing studies (NGS, GWAS) in different ethnic groups, indicating that many pathogenic genes may accumulate in each case of EA.

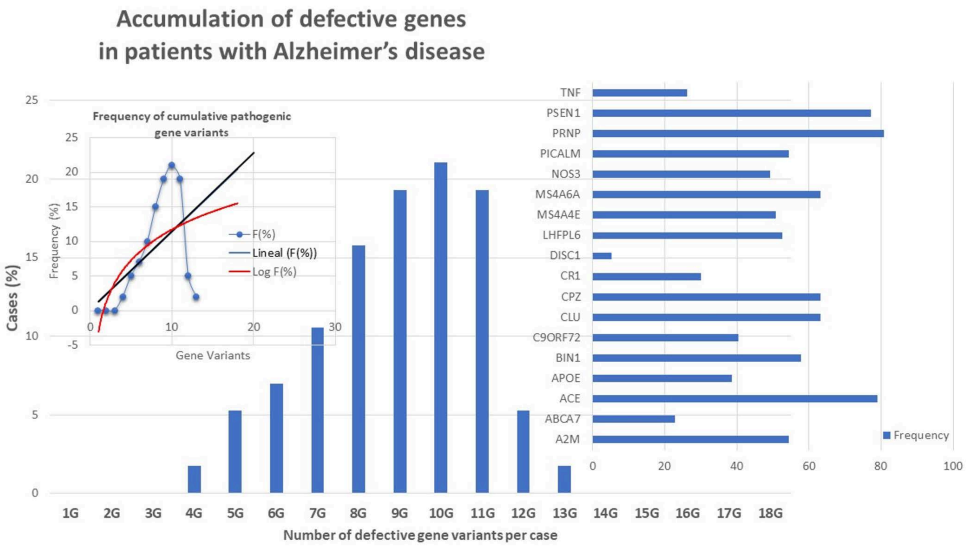
A very important aspect in the analysis of any genetic study in polygenic and complex diseases is to weigh the pathogenic load that each gene has in an individual case. Using a panel with the 18 most influential genes in AD and cerebrovascular disorders associated with dementia, in our AD cohort we found that (i) no patient is a carrier of a single pathogenic gene, (ii) most patients (> 60%) are carriers of several pathogenic genes (maximum frequency: 10 pathogenic variants per patient), (iii) a considerable number of cerebrovascular risk variants are present in the genotype of AD patients, and (iv) the genes that with greater frequency (> 50%) accumulate pathogenic variants in the same patient are A2M (54.38%), ACE (78.94%), BIN1 (57.89%), CLU (63.15%), CPZ (63.15%), LHFPL6 (52.63%), MS4A4E (50.87%), MS4A6A (63.15%), PICALM (54.38%), PRNP (80.70%) and PSEN1 (77.19%).

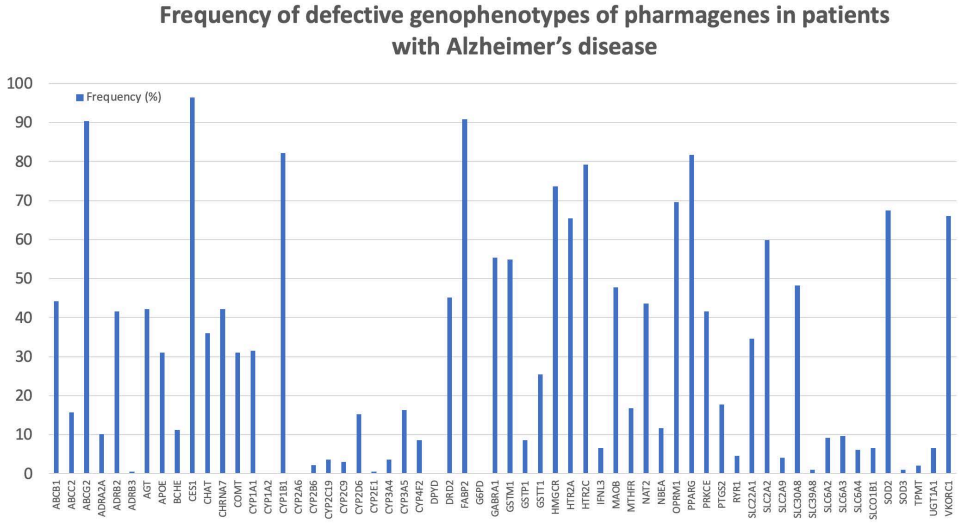
In relation to the pathogenic burden that the APOE-4 allele may represent in the clinical expression of AD and in its neuropathological phenotype, the pathogenic influence of the APOE-4 allele, from a quantitative point of view, does not affect more than 35-40% of AD cases. However, the pathogenic roles of the APOE-2/4, APOE-3/4 and especially APOE-4/4 genotypes are highly relevant. From multiple studies designed to characterize APOE-related AD phenotypes over the past 30 years, several conclusions can be drawn: i) the age of onset is 5-10 years earlier in approximately 80% of AD cases harboring the APOE-4/4 genotype; ii) serum levels of APOE are lower in APOE-4/4, intermediate in APOE-3/3 and APOE-3/4, and higher in cases of APOE-2/3 and APOE-2/4; iii) serum cholesterol levels are higher in APOE-4/4 than in the other genotypes; iv) HDL cholesterol levels are lower in APOE-3 homozygotes than in APOE-4 allele carriers; v) LDL cholesterol levels are consistently higher in APOE-4/4; (vi) triglyceride levels are significantly lower in APOE-4/4; vii) nitric oxide levels are slightly lower in APOE-4/4; viii) serum and cerebrospinal levels of Aβ differ between APOE-4/4 and the other more frequent genotypes (APOE-3/3, APOE-3/4); ix) blood histamine levels are drastically reduced in APOE-4/4 compared to the other genotypes; (x) brain atrophy and neuropathology of AD are markedly increased in carriers of APOE-4/4> APOE-3/4> APOE-3/3; (xi) brain activity slows down in APOE-4/4 carriers from the early stages of the disease; (xii) cerebral hemodynamics, reflected by reduced cerebral blood flow velocity and increased pulsatility and resistance indices, is significantly worse in APOE-4 than in APOE-3 carriers; cerebral hypoperfusion and neocortical oxygenation are also more deficient in APOE-4 carriers; (xiii) lymphocyte apoptosis is markedly altered in APOE-4 carriers; xiv) cognitive decline is faster in patients with APOE-4/4 than in carriers of any other APOE genotype; xv) in approximately 3-8% of AD cases, some dementia-related metabolic dysfunctions accumulate more in APOE-4 carriers than in APOE-3 carriers; xvi) some behavioral disorders, alterations in circadian rhythm patterns, and mood disorders are slightly more frequent in APOE-4 carriers; xvii) aortic and systemic atherosclerosis are also more frequent in APOE-4 carriers; xviii) liver metabolism and transaminase activity differ in APOE-4/4 carriers in relation to other genotypes; xix) hypertension and other cardiovascular risk factors also accumulate in APOE-4; and xx) APOE-4/4 carriers are the worst responders to

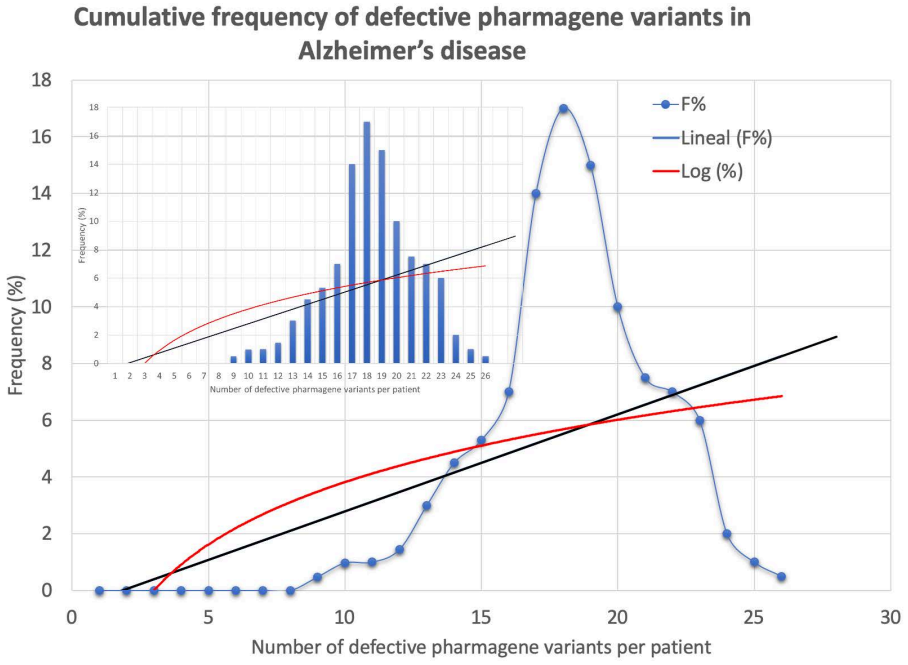
conventional drugs. These 20 main phenotypic characteristics clearly illustrate the biological disadvantage of APOE-4 homozygotes and the consequences that these patients may experience when receiving drug treatment for AD and / or concomitant pathologies. These findings confirm a golden rule in genomic medicine: the greater the number of genes affected, the earlier onset of the disease, the more accelerated course and the poorer the response to treatment; the fewer genes affected, the later onset of the disease, the slower the course and the better the response to treatment.

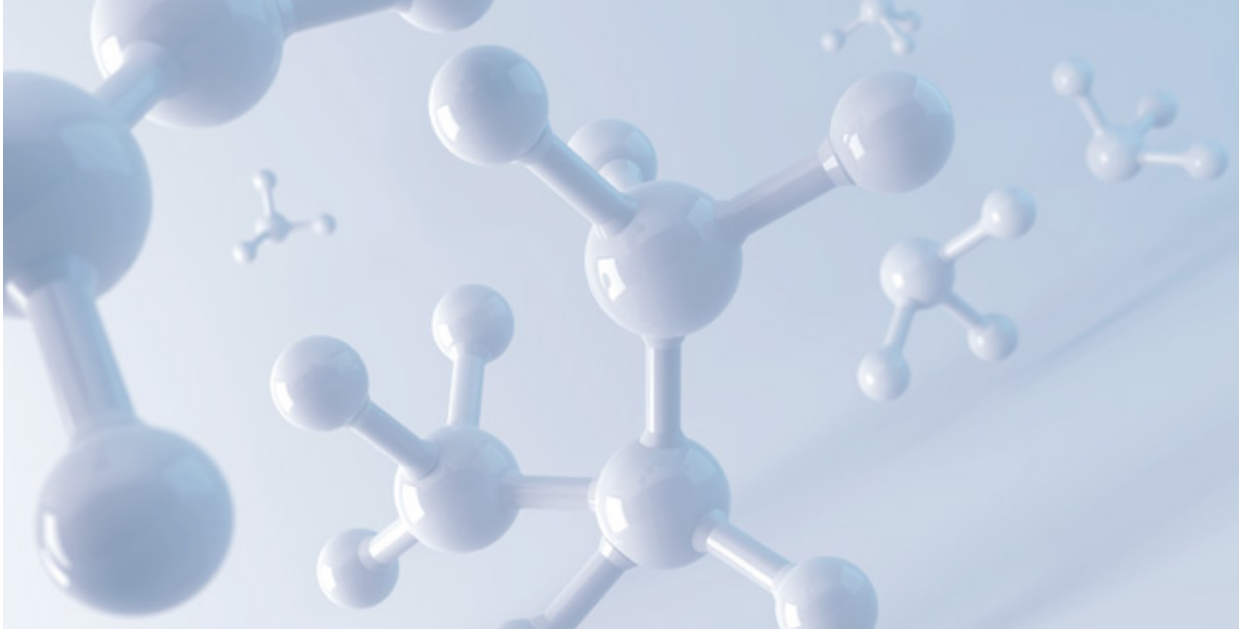





Accumulation of defective genes
in patients with Alzheimer's disease
Frequency of cumulative pathogenic gene variants
F(%)
Lineal (F(%))
Log F(%)
Frequency (%)
Gene Variants
Cases (%)
Number of defective gene variants per case
1G 2G 3G 4G 5G 6G 7G 8G 9G 10G 11G 12G 13G 14G 15G 16G 17G 18G
TNF
PSEN1
PRNP
PICALM
NOS3
MS4A6A
MS4A4E
LHFPL6
DISC1
CR1
CPZ
CLU
C9ORF72
BIN1
APOE
ACE
ABCA7
A2M
Frequency


Frequency of defective genophenotypes of pharmagenes in patients
with Alzheimer's disease
Frequency (%)
ABCB1 ABCC2 ABCG2 ADRA2A ADRB2 ADRB3 AGT APOE BCHE CES1 CHAT CHRNA7 COMT CYP1A1 CYP1A2 CYP1B1 CYP2A6 CYP2B6 CYP2C19 CYP2C9 CYP2D6 CYP2E1 CYP3A4 CYP3A5 CYP4F2 DPYD DRD2 FABP2 G6PD GABRA1 GSTM1 GSTP1 GSTT1 HMGCR HTR2A HTR2C IFNL3 MAOB MTHFR NAT2 NBEA OPRM1 PPARG PRKCE PTGS2 RYR1 SLC22A1 SLC2A2 SLC2A9 SLC30A8 SLC39A8 SLC6A2 SLC6A3 SLC6A4 SLCO1B1 SOD2 SOD3 TPMT UGT1A1 VKORC1


Cumulative frequency of defective pharmagene variants in
Alzheimer's disease
F%
Lineal (F%)
Log (%)
Frequency (%)
Number of defective pharmagene variants per patient
Number of defective pharmagene variants per patient



Xenoestrogenic Syndrome: The high price of contraceptives and hormone replacement therapy

Xenoestrogenic syndrome (XES) is a new clinical entity that we discovered in fertile women who have used contraceptives chronically (SXE type 1) and in perimenopausal women who have used hormone replacement therapy for years (SXE type 2). These women have a special genomic and pharmacogenetic profile that poorly tolerates estrogens and progestogens, which are part of commercial preparations, used as contraceptives in fertile ages of life and/or in menopause to alleviate the symptoms of this physiological condition. The massive tissue impregnation by estrogens produces important alterations in metabolism, causing a deficiency syndrome, with anemia, deficiency of folic acid and vitamin B_{12}, arterial hypertension, high risk of thromboembolism -with possible cardiovascular and cerebrovascular events-, increased risk of cancer, and alteration of higher functions of the central nervous system, characterized by emotional imbalance, anxiety and some cognitive impairment.

Estrogens are steroid sex hormones produced by the ovaries, placenta, and adrenal glands, under the control of the hypothalamic-pituitary-adrenal axis, through the hypothalamic neurohormone GnRH (gonadotropin-releasing hormone), which stimulates follicle-stimulating pituitary hormones (FSH) and luteinzing hormone (LH) and luteotropin). Estrogens are derived from androgens and progestogens, through the action of aromatase enzymes, giving rise to Estrone, derived from progesterone, Estradiol, derived from testosterone, and Estriol, derived from androsterone. The main female estrogenic hormones are estrone and estradiol, which regulate the menstrual cycle. Large amounts of estriol are produced with pregnancy, especially in the last trimester of pregnancy. Estrogens have multiple regulatory functions, affecting the menstrual cycle and pregnancy, the genitourinary system, the cardiovascular system, the synthesis and degradation of lipids, the musculoskeletal system, the breasts, dermal tissues, including hair, and the nervous system. Excess estrogen causes Hyperestrogenism, which can be caused by an exaggerated increase in estrogen (absolute hyperestrogenism) or a decrease in progesterone (relative hyperestrogenism).

The **therapeutic indications** for Estradiol and estrogens, as drugs, are treatment of moderate or severe vasomotor symptoms associated with menopause, vulvar and vaginal atrophy, hypoestrogenism (due to hypogonadism, castration or primary ovarian failure), prostate cancer, palliative of some types of breast cancer, prophylaxis of osteoporosis, uterine bleeding abnormal due to hormonal imbalance, and postmenopausal urogenital

symptoms of the lower urinary tract (urinary urgency, dysuria). Estrogens are not indicated during pregnancy or immediately after delivery. They decrease the quantity and quality of human milk.

Its **contraindications** include hypersensitivity to estradiol or any component of the formula, abnormal vaginal bleeding, thrombophlebitis and / or venous thromboembolic disorders, thromboembolic disease (for example, stroke, myocardial infarction), breast carcinoma, tumors estrogen-dependent liver disease or dysfunction, porphyria, and pregnancy.

Various **precautions** must be considered when consuming estrogens. Estrogens can increase the risk of breast cancer. The use of estrogen can lead to severe hypercalcemia in breast cancer and bone metastases. The risk of dementia may increase in postmenopausal women. Estrogens may increase the risk of endometrial carcinoma in postmenopausal women with an intact uterus. Estrogens can exacerbate endometriosis. Estrogen compounds are generally associated with lipid effects, such as increased HDL-C and decreased LDL-C. Triglycerides may also increase (use with caution in family defects of lipoprotein metabolism). Estrogens can cause retinal vascular thrombosis. Estrogens with or without progestin should not be used to prevent coronary heart disease. Extreme caution should be exercised in cases of cardiovascular disease or dysfunction. Caution should also be exercised when there is a history of cholestatic jaundice associated with estrogen use or during pregnancy. Fluid retention, asthma, diabetes, epilepsy, migraine, kidney dysfunction, gallbladder disease, hepatic hemangiomas, severe hypocalcemia, systemic lupus erythematosus, and porphyria can be aggravated by the use of estrogens. Whenever possible, estrogens should be discontinued for at least 4 weeks before and for 2 weeks after elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization. The absorption of topical emulsion and topical gels is increased by applying sunscreen. The transdermal patch may contain conductive metal (e.g., aluminum). Estrogens with or without progestin should be used for the shortest duration possible at the lowest effective dose, consistent with the goals of treatment. Care should also be taken when applying topical products to the severely atrophic vaginal mucosa.

The **adverse reactions** of estrogens are multiple in different systems and organs:

Cardiovascular Reactions: deep vein thrombosis, edema, hypertension, myocardial infarction, stroke, venous thromboembolism.

CNS Reactions: Anxiety, dementia, depression, dizziness, exacerbation of epilepsy, headache or migraine, insomnia, irritability, mood disorders, nervousness.

Dermatological Reactions: Angioedema, chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, scalp hair loss, melasma, pruritus, rash, urticaria.

Endocrine and Metabolic Reactions: Alterations in the frequency and flow of menstruation, breast cancer, breast enlargement, breast pain, breast tenderness, decreased LDL-C, fibrocystic breast changes, galactorrhea, glucose intolerance, hypocalcaemia, increased HDL-C, increased serum triglycerides / phospholipids, increased

thyroid-binding globulin, increased total thyroid hormone (T4), changes in libido, nipple pain, discharge vaginal, vaginitis, weight gain / loss.

Gastrointestinal Reactions: Abdominal cramps, bloating, abdominal pain, cholecystitis, cholelithiasis, diarrhea, flatulence, gallbladder disease, nausea, pancreatitis, vomiting.

Genitourinary Reactions: Changes in cervical discharge, dysmenorrhea, endometrial cancer, endometrial hyperplasia, enlargement of uterine leiomyomas, metrorrhagia, ovarian cancer, suspicious pap smear, urinary tract infection, uterine pain, vaginal yeast infection.

Hematological Reactions: Worsening of porphyria, decrease in antithrombin III and antifactor Xa, increase in factors VII, VIII, IX, X, increase in fibrinogen levels, increase in platelet aggregability, increase in platelet count, increased prothrombin.

Hepatic Reactions: Cholestatic jaundice, enlarged liver hemangioma, increased liver function tests (rare condition).

Local Reactions: Reaction at the application site, burning, erythema, irritation, thrombophlebitis.

Neuromuscular and Skeletal Reactions: Arthralgia, back pain, chorea, leg cramps, muscle cramps.

Ocular Reactions: Intolerance to contact lenses, steepening of corneal curvature, retinal vascular thrombosis.

Respiratory Reactions: Asthma exacerbation, pulmonary thromboembolism.

Other Reactions: Anaphylactoid/anaphylactic reactions, leg pain, toxic shock syndrome (vaginal ring).

There are approximately 20-30% of women who, due to their **pharmacogenetic profile**, should not consume estrogens. In these women, the uncontrolled use of estrogens can have serious consequences for their health, with exacerbation of the adverse reactions typical of estrogens.

Women with any of the following risk pharmacogenotypes should be especially careful: AKR1C4 (Leu311Val); APOE-2/4, 3/4, 4/4; CYP1A1*2C; CYP1A2-C734A and G-2964A; CYP1B1 (Val432Leu); CYP3A4*1, CYP3A4*1B, CYP3A4*2, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*8, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*15, CYP3A4*17, CYP3A4*18, CYP3A4*19, CYP3A5*3; CYP19A1: rs1902584; ESR1: rs2234693, rs3798577, rs9340799, rs728524; ESR2: CA repeats of D14S1026, rs1271572, rs1256049, rs1255998; F2: G20210A; F5: Arg506Gln; ITGB3: Leu33Pro (PlA1 or PlA2); MTHFR: Ala222Val (C677T).

Other **genetic mutations** that can affect the proper metabolization and effects of estrogens involve the following genes: ABCB11; ABCC2; ABCC3; ABCC8; ABCG2; ACACA;

ACOX1; ACSL1; ADIPOQ; ADRA2C; ADRB1; AGT; AGTR1; AHR; ALDH2; ALOX5; APOB; APOD; AR; ARG1; BRCA1; CCND1; CDA; CFH; CFTR; CHRNA4; CHRNB2; CNR1; COL1A1; CREB1; CYP4B1; CYP7A1; CYP11B2; CYP27A1; DTNBP1; EPHX1; ERBB2; ERCC2; F7; FGB; FKBP5; FMO1; FMO3; FOS; G6PD; GGH; GSK3B; GSTO1; GSTT1; HBB; HFE; HSD17B1; HTR2A; IL1B; IL4; IL6; IL8RB; ITGA2; KDR; KIT; KRAS; LIPC; LPL; MAOA; MAOB; MET; MMP2; MMP3; NOS3; NQO1; NR3C1; PDGFRA; PPARGC1A; PSEN1; PTGER3; PTGER4; PTGES; PTGFR; PTGS1; PTGS2; RB1; RRM1; SCARB1; SLC11A1; SLC15A2; SLC5A5; SLC6A3; SLCO1C1; SLC22A7; SULT1A1; SULT1E1; TGFB1; TNF; TNFRSF1B; TP53; TYMS; UGT1A1; UGT1A3; UGT1A4; UGT1A6; UGT1A7; UGT1A9; UGT1A10; UGT2B7; UGT2B15; VDR; VEGFA.

Estrogens are **major substrates** of the enzymes encoded in the ABCB1, ABCC1, COMT, CYP1A1, CYP1A2, CYP1B1, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 genes; and they are **minor substrates** of the enzymes CYP2A6, CYP2B6, CYP2D6, CYP2E1, CYP3A4 and UGTs.

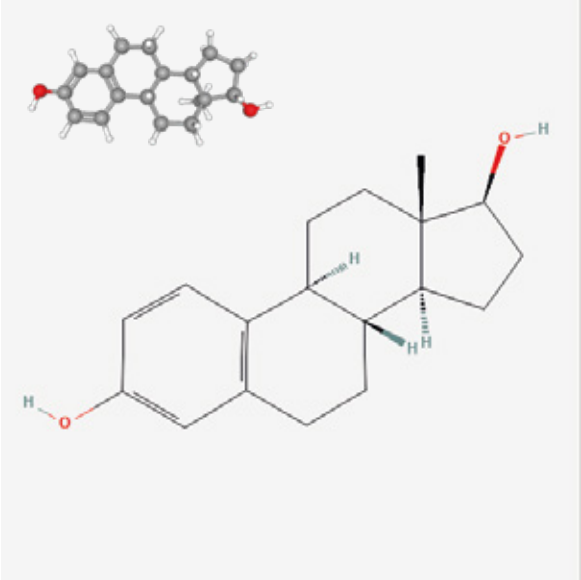
Under various conditions, estrogens can also act as **inhibitors** of the enzymes ABCB1, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4; and as **inducers** of CYP2A6 and CYP3A4 enzyme activity.

The complexity of the **pharmacogenetics of estrogens** means that they can interact dangerously with other drugs, causing high-risk reactions.

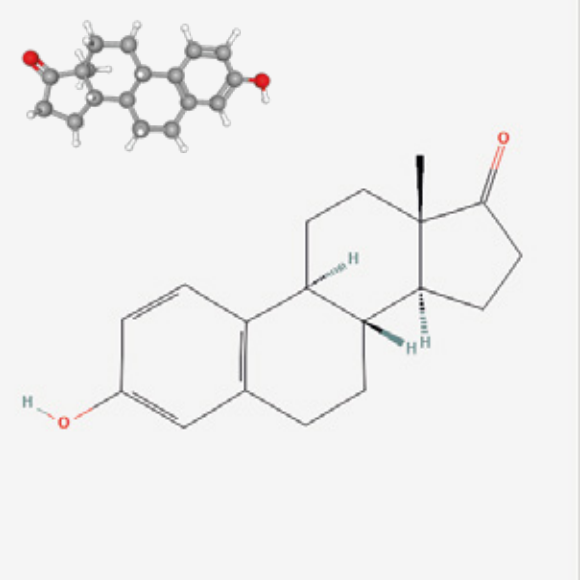
There are various **combinations of estrogens** with other drugs on the market. The most common are the combinations of Estradiol with Algestone, Cyproterone, Didrogesterone, Dienogest, Drospirenone, Hydroxyprogesterone, Levonorgestrel, Medroxyprogesterone, Norethindrone, Norgestrel, Prednisolone, Progesterone, Testosterone, Benzyl Benzoate, and Estradivgeston with Esteriol.

(*) For a better understanding of Pharmacogenetics, visit www.euroespes.com, consult the ***World Guide of Drug Use and Pharmacogenomics***, or check the properties and uses of the **EuroEspes Smart Pharmacogenetics Card**.

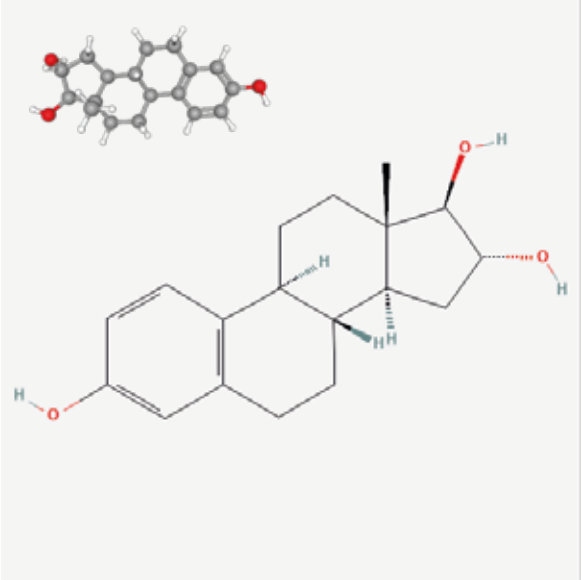
Estradiol



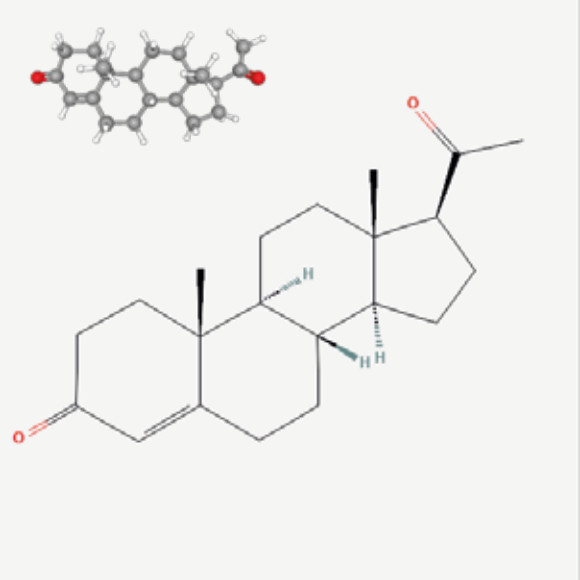
Estrone



Estriol



Progesterone

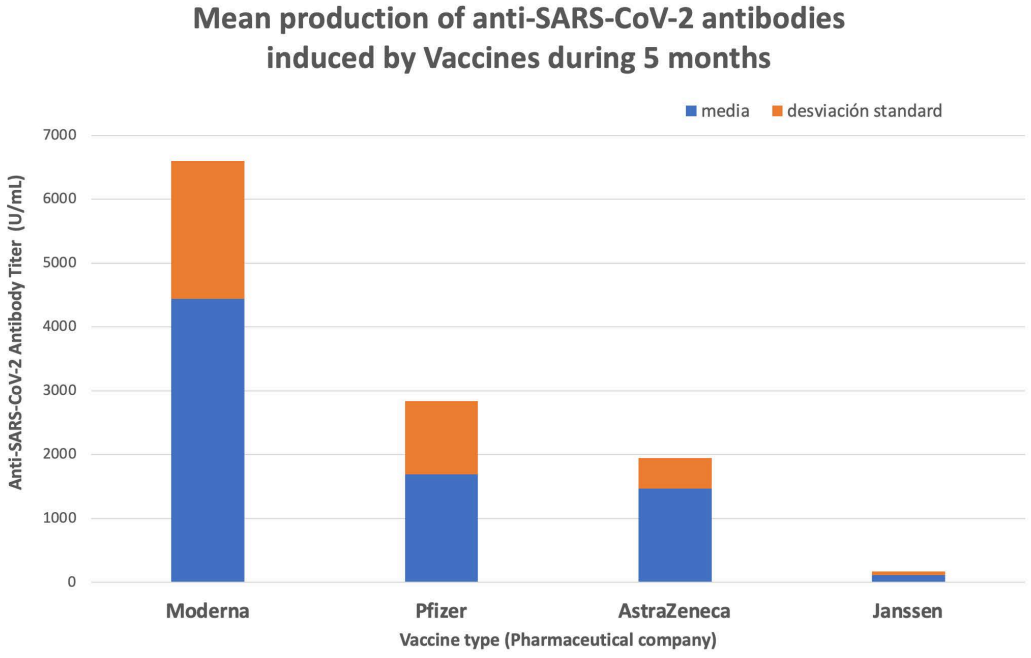


Covid-19 News

Immunogenicity power of anti-SARS-CoV-2 vaccines (Spain study)

The purpose of a vaccine is to generate antibodies against the pathogen we want to combat; and the individual immunogenic response depends mainly on three factors: genomic quality, immunological status and responsiveness of the immune system, and the immunogenic power of the vaccine in question.

In a cohort of 531 patients studied at the EuroEspes Medical Center by Lola Corzo and Susana Rodríguez, from the Clinical Analysis Laboratory of our institution, we analyzed the immunogenic power of the four anti-SARS-CoV-2 vaccines commonly used in Spain (Moderna, Pfizer, AstraZeneca, Janssen). The results are crystal clear. The average antibody titer generated by Moderna's vaccine during the 5 months following vaccination is 4440±2162 U/mL; the levels of antibodies generated by the Pfizer vaccine are 1693±1145 U/mL; those generated by the AstraZeneca vaccine 1471±479 U/mL; and those induced by the Janssen vaccine 118 ± 56 U/mL (see attached figure). Based on these results, it seems obvious - regardless of the genomics and the immunological status of each patient - that the vaccine with the highest immunogenic power is that of Moderna, followed by that of Pfizer and AstraZeneca, while that of Janssen gives very poor results.



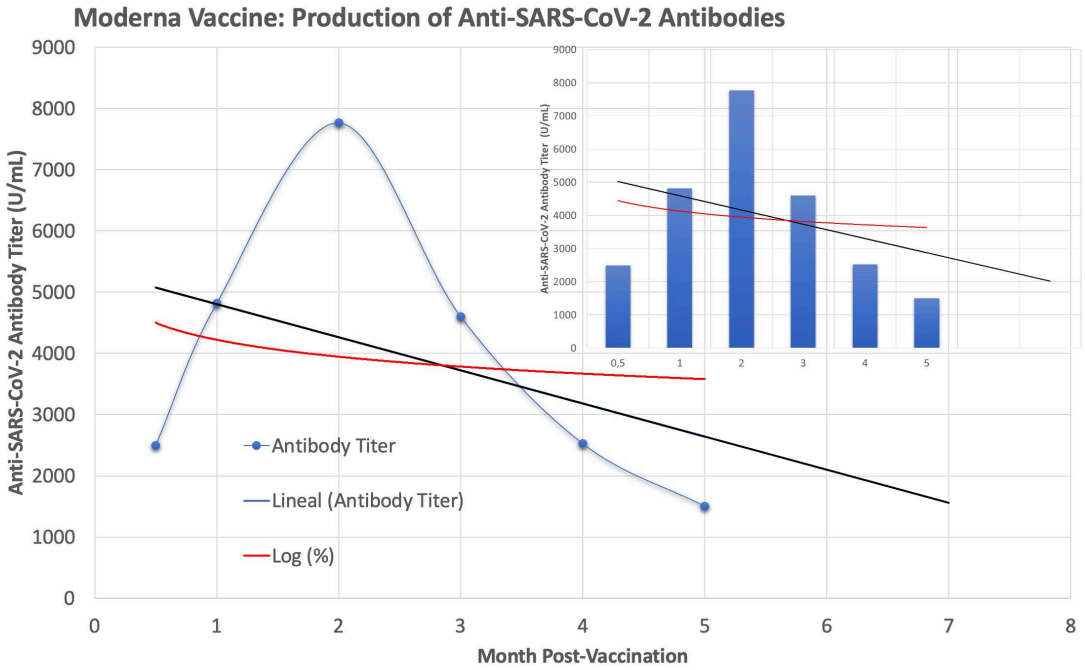
Post-vaccination Antibody Production by Moderna, Pfizer, AstraZeneca and Janssen after 5 months (Spain study)

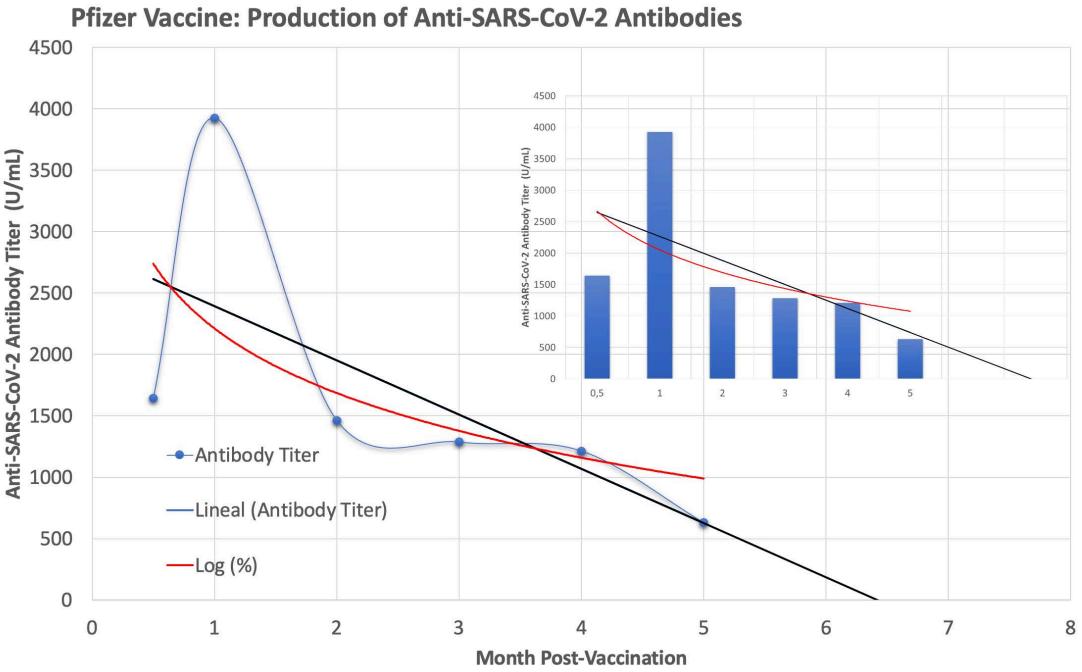
A fundamental aspect to assess the efficacy of a vaccine, in addition to its immunogenic power, is the time that the antibody titer remains at reasonable levels. Our casuistry shows how Moderna's vaccine generates a maximum peak of antibodies 3 months after vaccination, with a progressive decline in the following months. The Pfizer vaccine shows a maximum peak of activity one month after vaccination and then progressively declines. The peak of the AstraZeneca vaccine also occurs in the first month after vaccination but remains almost stable throughout the first 3 months following vaccination. For its part, the Janssen vaccine shows a poor and atypical pattern, with a similar peak of antibodies at 3-4 months after vaccination.

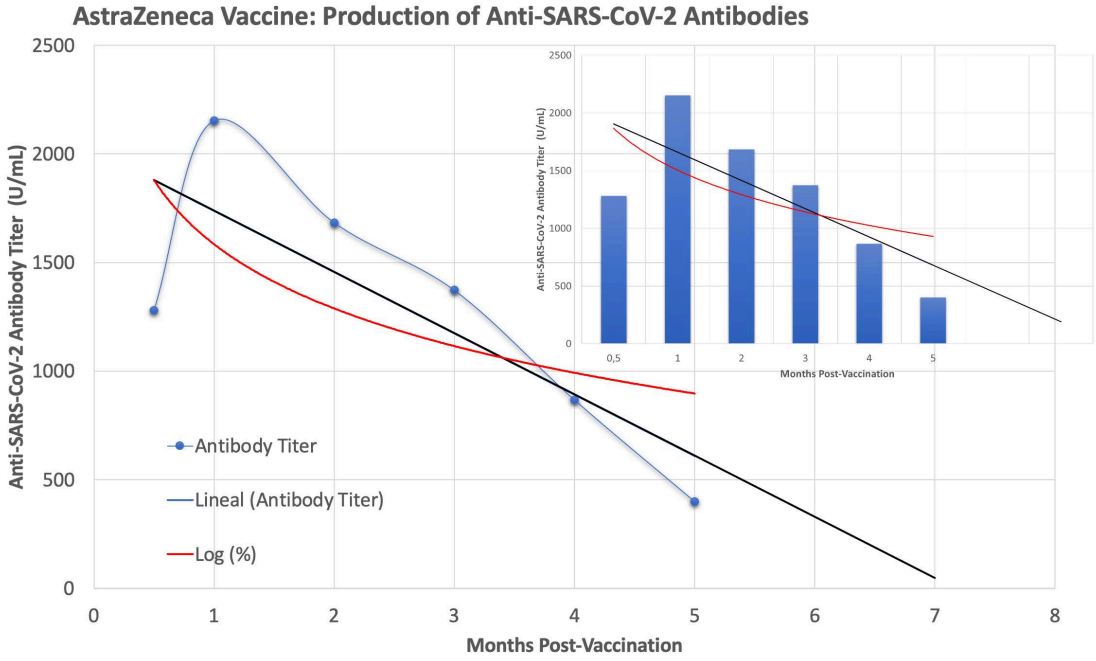
If we look at the attached figures, we can see that all vaccines show a similar pattern, with maximum peaks of antibodies between the first and third month after vaccination, that later gradually decline to levels of low immunity and, therefore, of unlikely immunogenic coverage against coronavirus invasion. Of the 4 vaccines studied, Moderna's is the one with the greatest immediate immunogenic power and the one that shows the most effect during at least the 5 months following vaccination. Obviously, when we consider the individual genomics and the immunogenic status of each patient, the antibody response is highly variable to any of the vaccines commonly used in Spain.

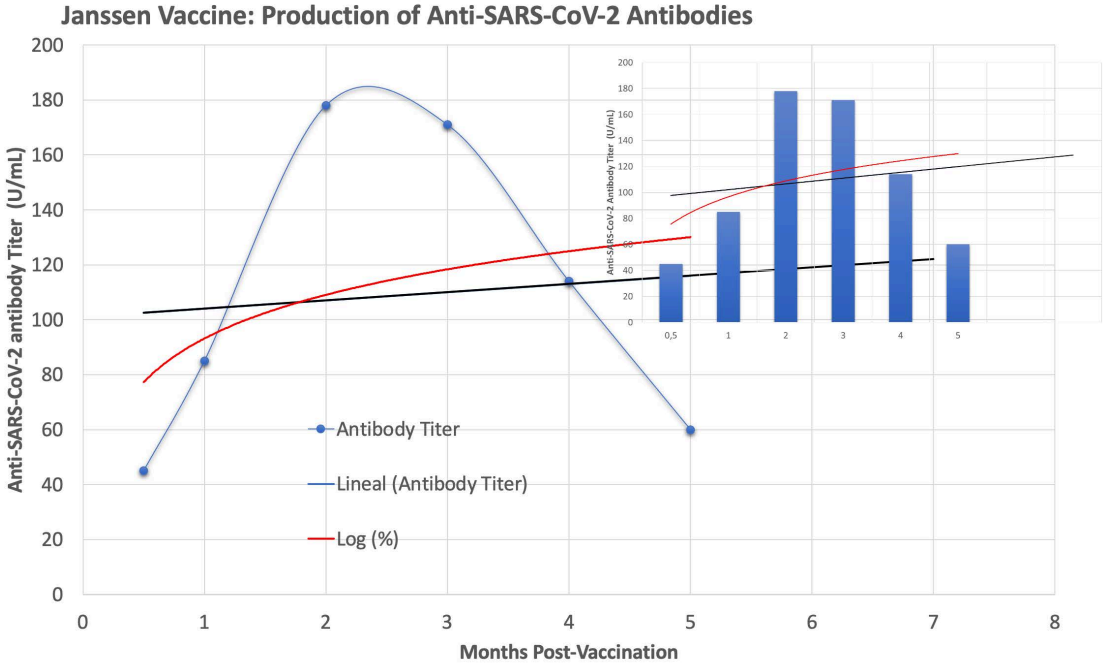
We insist on that the health authority should be concerned with analyzing the antibody titer of vaccinated people to know whether they are really immunized or not; otherwise, 20-40% of vaccinated people believe they are immunized without being immunized and, consequently, they are susceptible to being infected by coronavirus as they do not have the minimum antibody titer necessary to efficiently combat a potential SARS-CoV-2 infection.

Likewise, what seems evident in our cohort is that the vast majority of patients present an alarming decline in the level of antibodies after the fifth month, except for those vaccinated with Moderna's bioproduct. The analysis of cases of individuals vaccinated over 9-12 months ago shows that more than 80% of vaccinated people stop being immunized after one year.



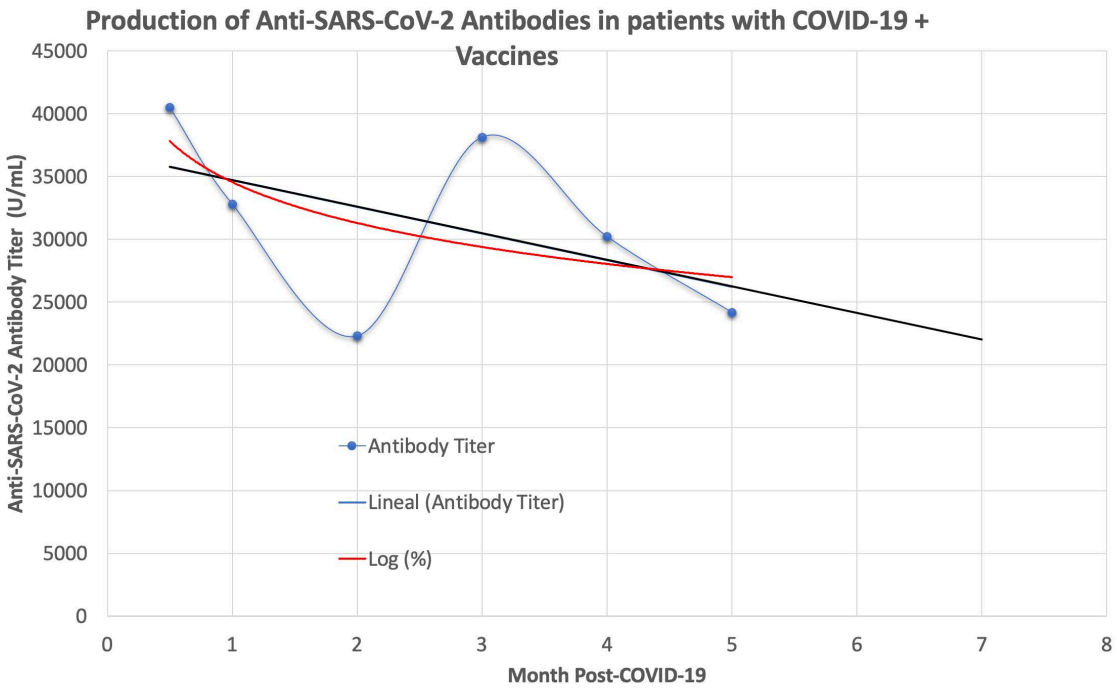

Pfizer Vaccine: Production of Anti-SARS-CoV-2 Antibodies
Anti-SARS-CoV-2 Antibody Titer (U/mL)
Month Post-Vaccination
Antibody Titer
Lineal (Antibody Titer)
Log (%)


AstraZeneca Vaccine: Production of Anti-SARS-CoV-2 Antibodies
Anti-SARS-CoV-2 Antibody Titer (U/mL)
Months Post-Vaccination
Antibody Titer
Lineal (Antibody Titer)
Log (%)


Janssen Vaccine: Production of Anti-SARS-CoV-2 Antibodies
Anti-SARS-CoV-2 antibody Titer (U/mL)
Months Post-Vaccination
Antibody Titer
Lineal (Antibody Titer)
Log (%)

Anti-SARS-CoV-2 antibody level in patients who have suffered COVID-19 and were subsequently vaccinated (Spain study)

Patients with COVID-19 in the infective phase show levels of antibodies per enzyme of 80,000 U/mL and only a few exceed 100,000 U/mL. Approximately, by the second or third month, these antibody titers have been reduced by half and in 20% of cases, the levels of antibodies are minimal from the ninth month or year after infection. These patients, even if they have passed COVID-19, can be reinfected, as can happen to those vaccinated but without antibodies. In those cases of infected patients who are administered an anti-SARS-CoV-2 vaccine from the second or third month after suffering the disease, regardless of the brand or type of vaccine, they show a spectacular increase in the titer of antibodies. This indicates that these patients, sensitized by the disease, respond powerfully to the vaccine. However, 3-6 months later, a progressive decline in the immune response begins, with a clear drop in antibody levels. Therefore, 10-20% of patients who have suffered COVID-19 and have been subsequently vaccinated are also susceptible to reinfection when their antibody titer disappears or is insufficient (see attached Figure).



EuroEspes, SA obtains the ARDAN 2021 Indicator as an Innovative Company and Equal Company in Gender

ARDAN has granted EuroEspes, SA recognition as an innovative company and equal company in gender, according to the 2021 indicators. ARDAN is a business information service developed by the Advanced Services Department of the Vigo Free Trade Zone Consortium (Galicia, Spain). This entity was founded in 1993, with the mission of making business information with high added value available to the public and developing support services around strategic information for making business decisions that lead to competitive improvement; it makes available to those responsible for business strategy useful information and techniques that allow comparing the evolution of the company with respect to its sector or competitors, both in the past and in anticipation of new policies and decisions. Its lines of action include a powerful and refined database of companies from all over Spain; economic reports, business listings and publications; economic studies; and the elaboration of collaboration projects with development agencies and diverse entities.

New lines of research for the use of Stem Cells in ME Health Cells, the Center led by Dr. Carlos Miramontes in Guadalajara, Mexico

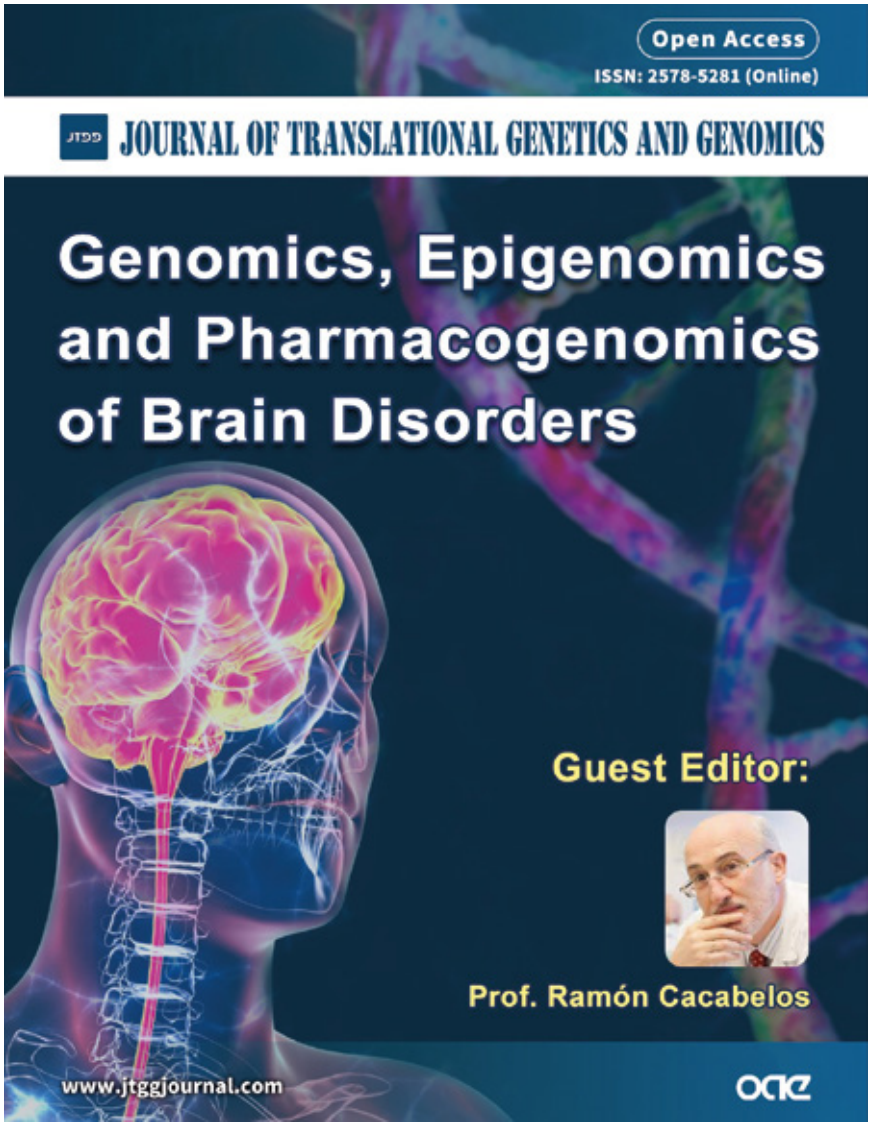
In 2013, EuroEspes signed a scientific and technical collaboration agreement for stem cell research with a Mexican group and with the Camilo José Cela University, when Dr. Ramón Cacabelos was Vice-Rector of Research and Science at that academic institution. In this month of October we have reviewed the evolution of that agreement with Dr. Carlos Miramontes, Director and Founder of *ME Health Cells* in Guadalajara, Jalisco, Mexico, a pioneering center in regenerative medicine with mesenchymal stem cells. The result of Dr. Miramontes' visit to the EuroEspes headquarters in Bergondo, A Coruña (Spain), is the launch of a new collaboration program for the development and research of new applications of mesenchymal stem cells in various human pathologies. Likewise, the industrial division of EuroEspes, Ebiotec, will participate in the preparation of different formulations to facilitate the application of stem cells for regenerative purposes.

Dr. Carlos Miramontes
with Dr. Ramón Cacabelos

Dr. Carlos Miramontes (left), with Laura Cid, Head of the Assistance Protocol Service, and with Francisco Álvarez, Financial Director of the EuroEspes Group.

Editorial News

Editions are open to the international scientific community for which Dr. Ramón Cacabelos is responsible, as Editor-in-Chief or Guest Editor for special issues dedicated to genomics, epigenetics, pharmacogenetics of diseases of the central nervous system and development of new pharmaceutical products.



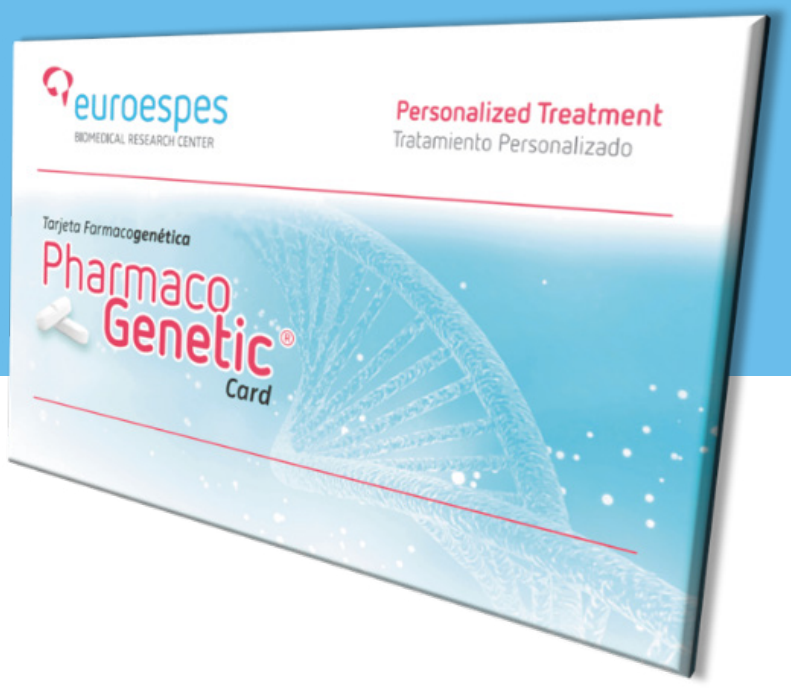
Promotional Section

Alzheimer's Prevention Plan (APP)
Home and Face-to-face

The APP identifies populations at risk of Alzheimer's disease (AD) and discriminates against other memory disorders and other forms of dementia. As the initial component of the APP is the identification of the genetic risk, in order to avoid unnecessary costs and discomfort due to the displacement of people, we have established a dual APP: (i) Home APP to perform genetic tests on a saliva sample that the interested person sends to the EuroEspes Medical Center with no need to travel; and (ii) face-to-face APP for those who wish to complete a complete diagnostic protocol, including genetic tests, at our Medical Center. Those people whose home APP detects an obvious risk can later join the face-to-face APP to complete the diagnostic set and enter the personalized prevention program through pharmacogenetic intervention.

Parkinson's Prevention Plan (PPP)
Home and Face-to-face

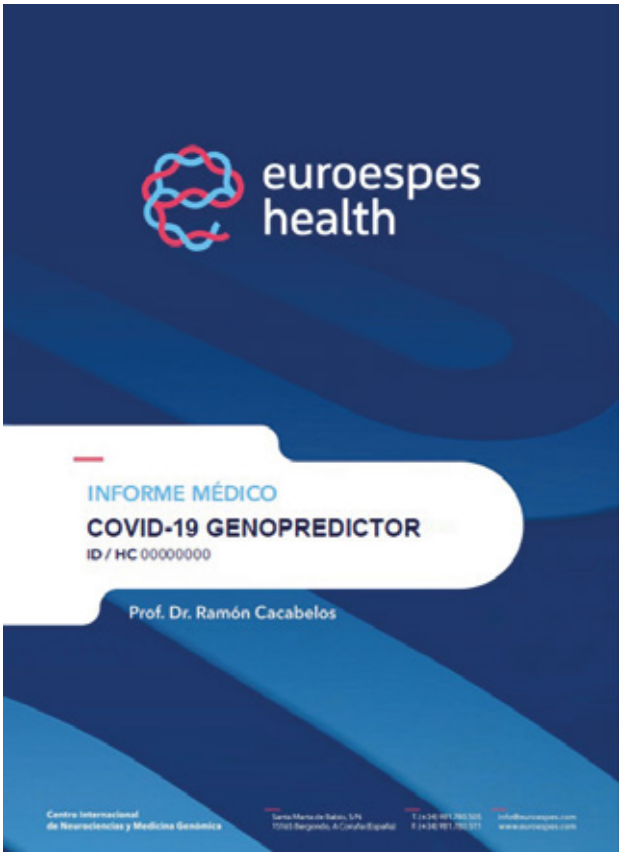
The PPP identifies the population at risk of suffering from Parkinson's disease, differentiating familial Parkinson's disease and other forms of parkinsonism (vascular, toxic or traumatic). The PPP also includes (i) a home PPP for all those asymptomatic people with a family history of Parkinson's or who detect incipient symptoms of tremor, rigidity or bradykinesia; and (ii) a PPP in person at the EuroEspes Medical Center where they would carry out the complete diagnostic protocol, including genomic screening. Patients following the home regimen who show genetic or environmental risk for Parkinson's would take the in-person PPP to complete the diagnostic set, and start the personalized prophylactic plan according to their pharmacogenetic profile.



Smart Pharmacogenetic Card PGx-60/4000

The most advanced bioinformatics product in the world with its personalized pharmacogenetic profile:

- to know the medicines you can take and which you should not take
- so that your doctor knows which drugs to prescribe and which drugs harm you
- to avoid toxicity and side effects when you have to take medication for any health problem
- to avoid life-threatening drug interactions if you have to take several medications simultaneously for long periods of time
- to avoid unnecessary expenses on products that are not useful to you
- to preserve your health with the appropriate medication for your genomic profile
- for the health of their children, who share 50% of their genome
- for life, because your genome does not change



COVID-19 GenoPredictor

The COVID-19 GenoPredictor is the only genetic test in the world that allows predicting vulnerability to SARS-CoV-2 infection with potential lung damage, immunological status and immune response capacity to coronavirus infection, and pharmacogenetic profile that allows us to personalize the pharmacological treatment appropriate to the genome of each person in case of need for treatment.

Carrying out this genomic test is recommended for people at high risk (heart disease, lung disease, hypertension, diabetes, stroke, cancer, immunosuppressed), people exposed by the nature of their work (high public attendance centers, frequent trips), people with a family history of risk, people infected by coronavirus and health personnel.

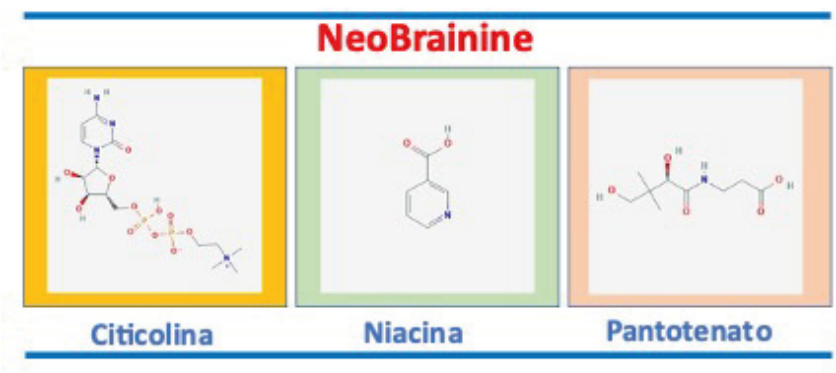
NeoBrainine

NeoBrainine is a new neuroprotective product for the prevention and treatment of various types of dementia and cerebrovascular risks (migraine, cerebral ischemia, thromboembolic events, stroke). NeoBrainine is a hybrid bioproduct, created by the team of scientists led by Dr. Ramón Cacabelos, that integrates citicoline, pantothenic acid and niacin molecules. Citicoline is a choline donor, acetylcholine precursor -an essential neurotransmitter for memory-; it is an essential component of the phospholipids of neuronal membranes and is an intermediate metabolite in nucleotide synthesis.

Pantothenic acid (D (+) - N- (2,4-dihydroxy-3,3-dimethylbutyryl) β-alanine) is an amide between pantoic acid with β-alanine; it is a water-soluble vitamin of the B complex, also known as vitamin B5 or vitamin W, essential for life. Pantothenic acid is a fundamental cofactor in the synthesis of coenzyme A (CoA) and in the metabolism and synthesis of carbohydrates, proteins and fats.

Niacin or nicotinic acid ($C_6H_5NO_2$) is another water-soluble vitamin of the B complex (vitamin B3, vitamin PP) involved in cell metabolism as part of the coenzyme NAD (nicotine-adenine-dinucleotide) and NAD-phosphate (NADP). Its derivatives (NADH, NAD+, NADPH, NADP+) are essential in energy metabolism and in DNA repair. Its main amide is nicotinamide or niacinamide ($C_6H_6N_2O$). Niacin is essential in the synthesis of steroid hormones and in the elimination of toxic xenobiotic agents.

The components of NeoBrainine (Citicoline, Niacin and Pantothenic Acid) exert essential neuroprotective functions for the normal functioning of the central nervous system.



Atremorine capsules

Atremorine has been approved by the European Patent Office for the prevention and treatment of Parkinson's disease.

In its usual presentation, Atremorine is dispensed as a powder to take with yogurt or other similar food, but not with water or liquids that can oxidize it or alter its properties. To avoid the use of powder and to facilitate the intake of Atremorine, EuroEspes Biotecnología (Ebiotec) launches Atremorine in capsules. The new presentation is now available nationally and internationally.

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DefenVid-90

EuroEspes Biotechnology (Ebiotec) launches a new presentation of DefenVid with 90 capsules. This new presentation covers a complete monthly treatment regimen. Ebiotec continues to maintain the presentation of 30 capsules.

DefenVid is an immunity enhancer epinutraceutical to combat immunodeficiency states or the fall in natural defenses associated with the use of antibiotics for bacterial infections or chemotherapeutic agents in cancer patients.

DefenVid is a powerful enhancer of cellular immunity at any age against viral infections.

The two presentations of 30 and 90 capsules are already available nationally and internationally.

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Complete Sequencing of the Human Genome

The team of geneticists from the Department of Genomics and Pharmacogenomics, led by Dr. Juan C. Carril and Dr. Óskar Martínez de Ilárduya Ruiz de Larramendi, Head of the Genomic Sequencing Unit, make available to users of medical services from the International Center for Neurosciences and Genomic Medicine, as well as from the national and international medical and scientific community, a service specialized in the complete sequencing of the human genome (> 20,000 genes) with NGS technology.

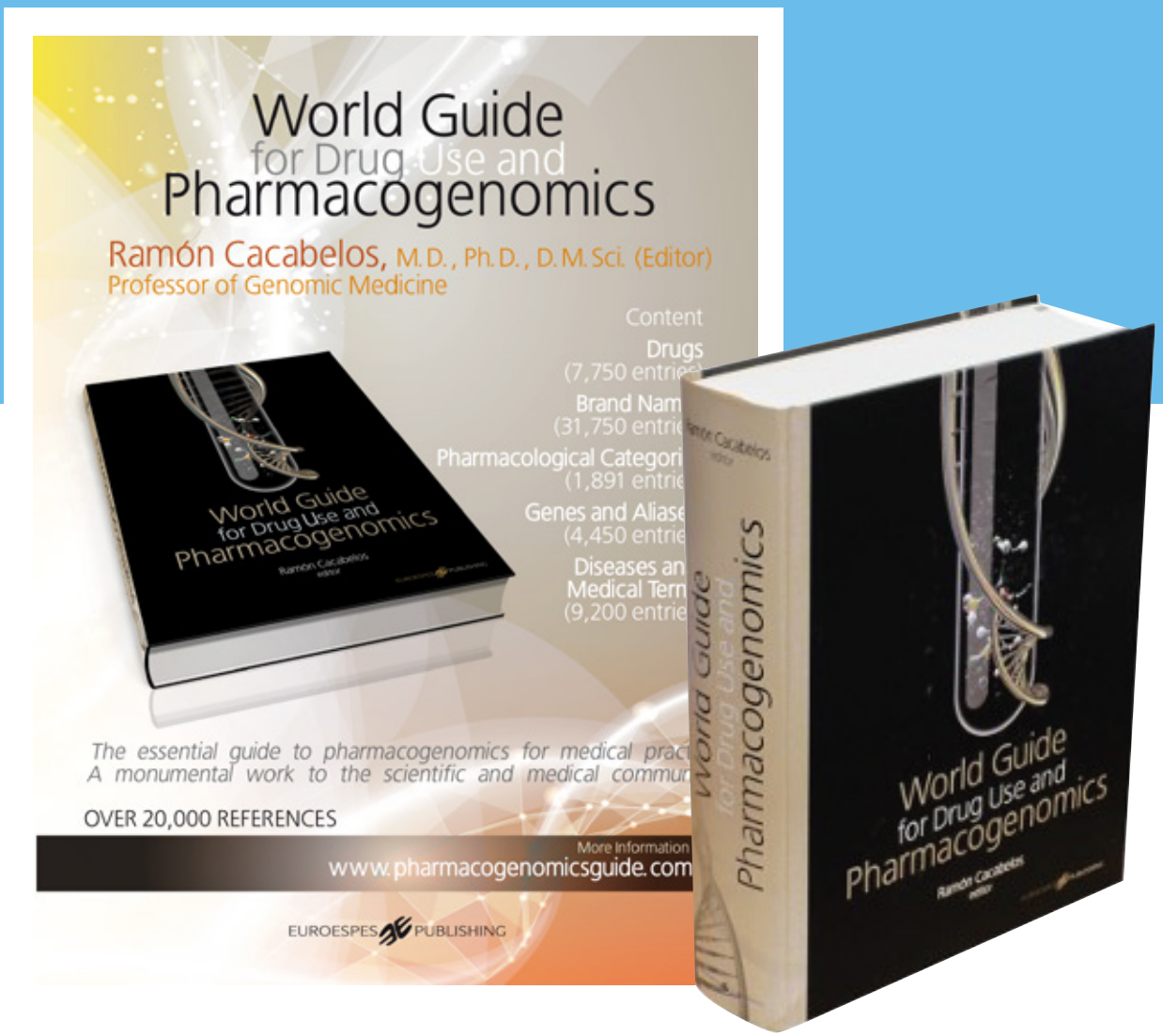
DermoGenetics Catalog

The Genomics and Pharmacogenomics Department of the EuroEspes Medical Center offers doctors and specialists in Dermatology the EuroEspes DermoGenetics Catalog. The Catalog includes the 1000 most relevant genes in skin diseases, from allergic reactions to skin cancer. This is the first Dermogenetics Catalog available in Europe.

Home Care: COVID-19 and Genetic Testing

Following our Community Care policy, facing the COVID-19 crisis, mobility restrictions in various national territories, and the difficulties of displacement of our national and foreign patients, the International Center for Neuroscience and Genomic Medicine has established a Home Care Service to our patients, to individuals and companies to carry out COVID-19 tests (PCR, Antigens, Antibodies) and genetic tests (see catalog at www.euroespes.com).

Phone No.: (+34) 981 780505.



World Guide for Drug Use and Pharmacogenomics

The First World Guide of Pharmacogenomics, edited by Dr. Ramón Cacabelos, incorporates for the first time the pharmacogenetic profile of commonly used drugs. In its more than 3000 pages the WGDUPGx catalogs (i) drugs approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Koseisho (Japan) and other international agencies, with their bioactive properties, side effects, metabolism and pharmacogenetic profile; (ii) genes of interest in human pathology and pharmacogenetics; and (iii) more than 9,000 illnesses and medical terms.

The World Guide for Drug Use and Pharmacogenomics is a fundamental reference in the library of universities, hospitals, medical departments and research centers.

Available from EuroEspes Publishing Co., Tel. (+34) 981 780 505.

EuroEspes Health Medical Bulletin

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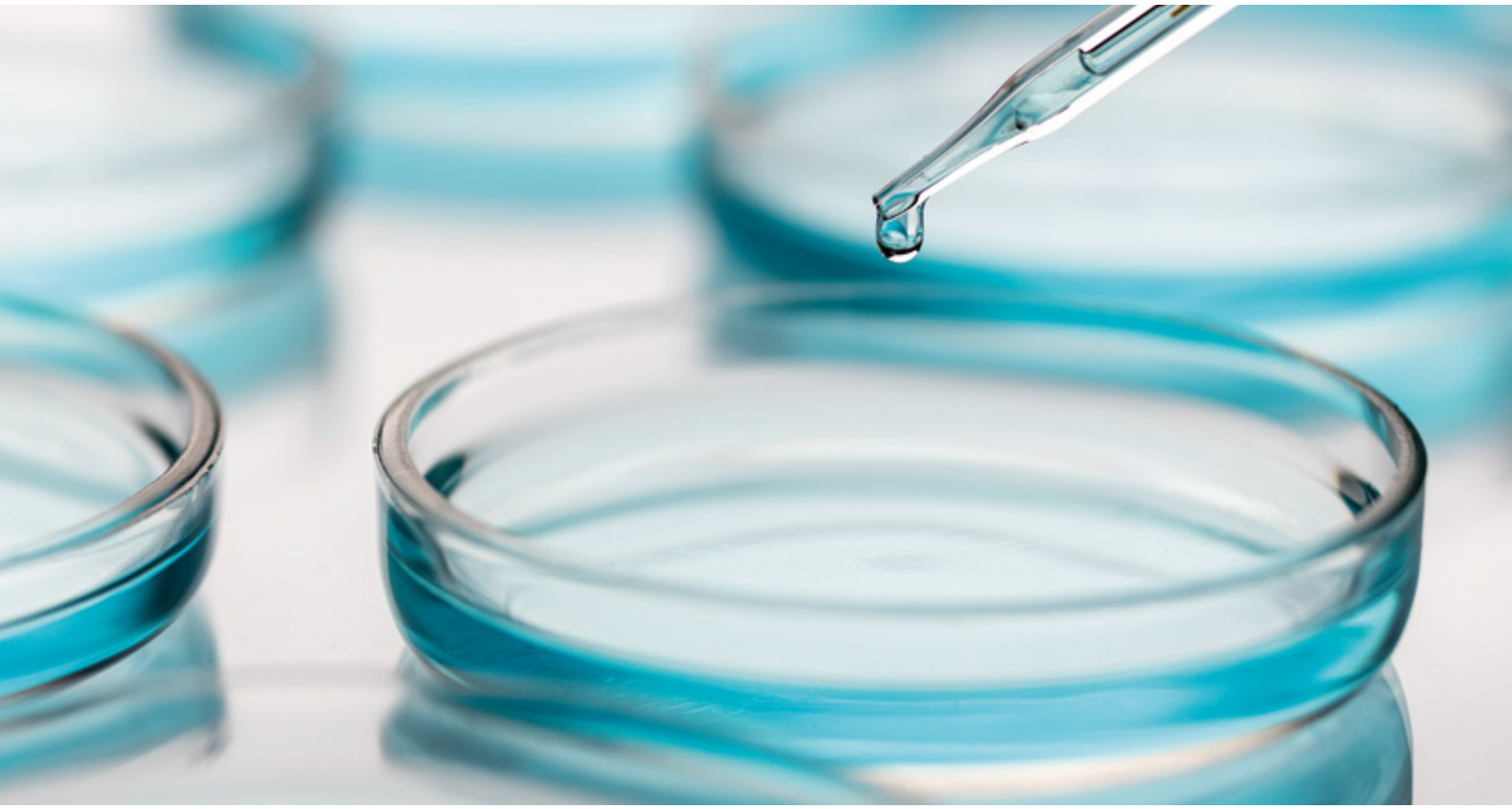
Photocomposition and Design: Chalana



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