euroespes health

Vol. 15 / August 2021

EuroEspes Health Medical Bulletin

International Center of Neuroscience
and Genomic Medicine

Contents

August Editorial

It Would Be Wise to Remember

When a public health problem becomes a crisis of the State, something does not work between the government, population, science, medicine and the media; and if the crisis transcends the professional frontier and becomes a public debate, taking over the front pages of newspapers and TV news, apart from infesting the social media pool with confusion, then, most likely, politicians and journalists are talking too much and doctors and scientists are talking too less (or both at the same time).

The COVID-19 pandemic is a regrettable example of informational toxicity, the result of the clumsiness and erratic behavior of the political authority and the daring of everyday opinion-makers who talk about everything and yet talk about nothing; therefore, a health problem, which should be under the professional tutelage of science and medicine, is under the government of political and media interest, with the consequent gradual increase in confusion and misinformation (in an interested or ignorant way).

Assuming the novelty factor, fear, lack of knowledge and the urgency to solve an unprecedented crisis as natural, many mistakes of the past could be excused; but after a year of traumatic experience for the population, various political experiments in each country, the negligence of Central Governments, the excessive and irresponsible appetite of the pharmaceutical industry, the belligerent attitude of denialist and enlightened groups and the neglect of the official medical services, it is convenient to recapitulate and rigorously analyze the course of events since last spring in order to avoid making the same mistakes in the months following this summer.

The summer disruptions are an anesthetic injection that cultivates temporary forgetfulness of the real problems, which will reappear by September. Now, the heat, the beach, reunion with

friends and family, the price of electricity, the mourning of the *Rolling Stones* for the loss of drummer Charlie Watts or the catastrophe in Afghanistan, already advocated in season 4 of the series *Homeland*, give fuel to the diverse debates of the summer season. Real life reappears with the return to work and school, limitations to travel, restrictions on leisure, the hypertrophic accumulation of delays in the Courts of Justice, the irresponsible impersonality of telematic medicine, non-deliveries due to transport problems, the payment of payrolls, the end-of-the-month difficulties to meet debts and financial commitments, and the infectious whims of each municipality set on fire by the political-justice dialectic to restrict freedoms.

From an epidemiological point of view, people wonder how a year ago the State of Alarm was so essential while those who defended them before now despise them. Once the political card of vaccination has been played, people wonder about the fifth wave, which appears in parallel with mass vaccination, as if vaccines were not as redemptive as the oracles advocated. Herd immunity (>70%) would solve the problem; however, with 80% of the population vaccinated in some countries (or more than 80%, like in Israel), the infections do not stop. 20% of people suffer asymptomatic COVID; 10-15% of those vaccinated are reinfected because no health ministry bothered to analyze the antibody titer that confers immunity to those vaccinated; a year ago, self-tests were a crime and no private laboratory could do what the wise officials of the Ministry of Health did not authorize, while now the tests are sold in any pharmacy and everyone interprets them as they like. A third dose of vaccine is already being considered without firstly clarifying why the second dose does not work in 10% of the population. The vaccination passport has been implanted by decree, without consulting the citizens; speculation with the establishment of a forced vaccination regulation is nonsense when there are still not enough vaccines for those who wish to be vaccinated freely; every decision is improvised repeatedly and unilaterally, without a unified health policy in a territory that brags about being called the European Union. The WHO remains at the rear, avoiding falling into past stupidities; the FDA continues defending North American interests; the EMA doubts what is its own and what is foreign; and each country is adopting its own solutions based on the criteria that its experts propose, with their own vaccines, such as Russia and China, and with their own policies, such as Israel, the USA and the rich Arab world. The pandemic is global, but the policies are tribal.

After the initial period of terror, the fear dissipates; the disbelieving population is shaking off the complexes and assumes that it is necessary to learn to live with the bug, that it is still there, that it will continue to mutate; and the delta variant will be followed by many other variants, until the human immune system learns to defend itself and instead of 10% asymptomatic, the figure rises to more than 50% and then vaccines will no longer be the holy grail which all the tormented want to drink from to get away from the apocalypse.

The press will continue to tell stories, as the business goes. Science will run its course, slowly but surely, preaching in the desert and selling itself to the highest bidder. Medicine will timidly reopen doors to the usual pathologies, which are the ones that really continue to kill people. Companies will have to overcome, rebuild and even relocate to prevent the spread of corpses in the labor cemetery from continuing. And politicians, showing off their flattering hieraticism, will announce that they have defeated the virus, looking for new propaganda for the upcoming plebiscite.

In the meantime, it would be wise to remember ...

Ramón Cacabelos
Professor of Genomic Medicine

Change of Therapeutic Paradigm in the Treatment of Alzheimer's disease

Alzheimer's disease is one of the main causes of morbidity, mortality and disability in people over 65 years of age, assuming high socio-economic and family costs in advanced countries. Each patient with Alzheimer's disease has an estimated cost of €15,000 to €30,000/year, depending on the evolution of the disease and the concomitant pathologies that the patient may suffer. Likewise, each Alzheimer's patient consumes between 6 to 12 different drugs daily, with the consequent risk of side effects. Pharmaceutical outlay in the Alzheimer's population represents 15-20% of the direct costs of the disease.

Alzheimer's disease is caused by the premature death of neurons. Multiple genomic defects (more than 600 defective genes in the human genome), epigenetic aberrations (DNA methylation, histone and chromatin changes, dysregulation of gene expression mediated by microRNAs), chronic brain ischemia and hypoperfusion, and various environmental factors (toxicity, microtrauma), are responsible for the accelerated neuronal death process in susceptible people.

Cerebral neuropathology is characterized by the presence of neuritic plaques with deposits of β-amyloid protein, neurofibrillary tangles resulting from hyperphosphorylation of the Tau protein, dendritic dearborization, and gradual loss of neurons in critical areas of the brain, such as the hippocampus and neocortex. This brain damage gives rise to the prevalent symptoms of the disease: memory loss, dyspraxia, aphasia, temporal-spatial disorientation, behavioral disturbance and progressive functional decline.

Alzheimer's affects about 50 million people worldwide, is more frequent in women than in men and its prevalence increases from 1.5% at 65 years of age to more than 35% in those over 80 years of age.

In the last 20 years, more than 10,000 products with a potential antidegenerative effect have been investigated for the treatment of dementia; however, from 1993 to 2003 only 4 drugs were approved. Tacrine was approved in 1993 and later withdrawn for causing severe liver toxicity. Tacrine was followed by the new generation of anticholinesterase agents to enhance cholinergic neurotransmission in memory circuits (Donepezil, Galantamine, Rivastigmine); and in 2003 Memantine, a product with inhibitory action on glutamate receptors, was approved to reduce neuronal excitotoxicity.

Since then, no new drugs were approved until July 2021, when the FDA (*U.S. Food and Drug Administration*), pressured by the powerful US Alzheimer's association, decided to approve the antibody Aducanumab, designed as a potential preventive agent to delay the onset of Alzheimer's disease.

With the introduction of Aducanumab to the market, the FDA is proposing a revolutionary change in the treatment of Alzheimer's disease. The change is logical because the death of neurons that gives rise to Alzheimer's begins 2-3 decades before the patient shows symptoms, in such a way that when cognitive deterioration occurs, the number of dead neurons is so significant that no treatment would be capable of reversing the damage, since neurons do not multiply and dead ones cannot not resuscitated. Therefore, the approval of prophylactic treatments may be conceptually sound, but catastrophic in economic terms, since it is estimated that the annual cost of a treatment with Aducanumab can rise to more than $40,000 per year, which would double the annual cost of the illness. This cost is unaffordable by the states and would have to be borne by each patient, which would generate more therapeutic inequality between rich and poor citizens. Furthermore, it is estimated that immunotherapy would only be useful in 10-20% of patients.

Since the initiative has already been launched, in the coming years there will be an explosion in the research of new drugs for Alzheimer's disease, from vaccines to preventive treatments with different therapeutic options. For this research to be successful - avoiding the debacle of the last 20 years - it will be necessary to choose the models of animal experimentation very well. To this end, at the request of the Taylor & Francis Editorial in London, responsible for the journal *Expert Opinion on Drug Discovery*, Dr. Ramón Cacabelos and his team have presented a study that shows all the animal models used in Alzheimer's research over the past 20 years. This study details the selection of each model based on the drug to be developed. Transgenic animals, in which the Department of Health Biotechnology led by Dr. Iván Carrera is an expert, are the favorites to reproduce the neuropathological characteristics of Alzheimer's disease in the laboratory, and for testing products capable of preventing premature neuronal death that over decades has destroyed the brains of patients with genomic risk.

This new generation of preventive drugs and bioproducts requires genomic characterization of patients to start treatment at least a decade before the disease manifests. In addition, the personalization of treatment should be systematically implemented through pharmacogenetic protocols in which the International Center of Neurosciences and Genomic Medicine EuroEspes is an expert and has been carrying out for the last 20 years.

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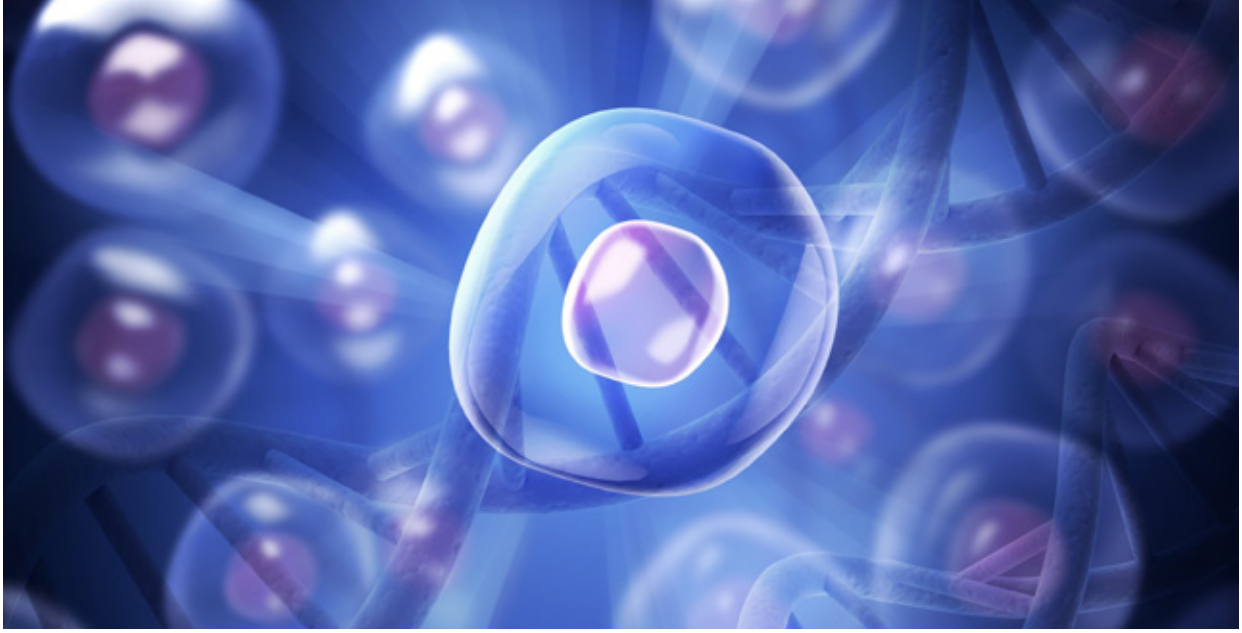

Oncogenic Stem Cells

Despite the powerful investment of human, scientific and financial resources in cancer research, this syndromic entity, which includes hundreds of neoplastic forms, continues to be one of the main causes of morbidity and mortality in the world, with approximately 20 million cases. In the USA, the most common type of cancer is breast cancer, with more than 279,100 new cases/year, followed by lung cancer and prostate cancer.

According to the epidemiological studies of the National Cancer Institute of the North American NIH, the number of new cases/deaths of the most frequent types of cancer are the following: Colon and rectum, 147,950 cases/53,200 deaths; Endometrium, 65,620/12,590; Liver and bile duct, 42,810/30,160; Leukemia (all types), 60,530/23,100; Non-Hodgkin's Lymphoma, 77,240/19,940; Melanoma, 100,350/6,850; Pancreas, 57,600/47,050; Prostate, 191,930/33,330; Lung (and bronchi), 228,820/135,720; Kidney (renal cells and renal pelvis), 73,750/14,830; Breast (women+men), 276,480+2,620/42,170+520; Thyroid, 52,890/2,180; and Bladder, 81,400/17,980.

The early detection of cancer is essential for the rapid implementation of the most effective treatments (surgery, chemotherapy, radiotherapy). However, a small subpopulation of cells has been detected in various tumors that are resistant to therapy and remain within the tumor. These cells grow and cause recurrence and metastasis of new tumors, and are known as cancer stem cells (CMC). After years of research, it has been possible to establish that CMCs are responsible for tumor initiation, progression, metastasis, and recurrence. CMCs represent a tumor cell subpopulation, with properties similar to those of other stem cells, but with an oncogenic capacity, to differentiate into various forms of cancer. CMCs are easily renewed and generate heterogeneous lineages of cancer cells resistant to conventional treatments. They also have the ability to migrate to other territories to give rise to new metastatic tumor niches. Recent studies have shown that the CMC population and cancer progression are increased by the dysregulation of different epigenetic pathways that have effects on gene expression patterns and key pathways related to cell proliferation and survival. Epigenetic modifications (DNA methylation, chromatin and histone changes, microRNA dysfunction) have been revealed as key drivers in the formation and maintenance of CMCs. Therefore, the

identification of CMCs and the characterization of the epigenetic pathways that regulate them may offer new insights into cancer treatment. A new line of anti-tumor therapeutic research is the development of epigenetic drugs and epinutraceutical byproducts for the prevention and treatment of various types of cancer.

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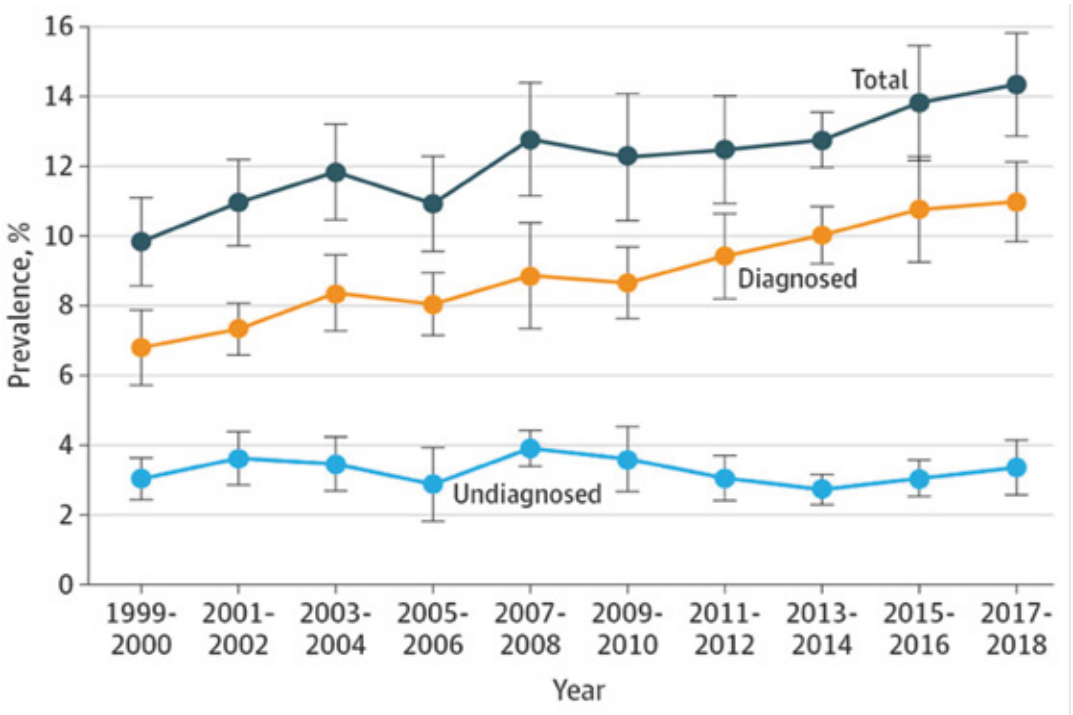
Alarming Increase in Diabetes

Diabetes is a global health problem, with about 425 million affected people, in an age range of 20 to 79 years (9%), according to the International Diabetes Federation. The distribution of diabetes shows a distinct geographic pattern. In the United States, an estimated 34.2 million people have diabetes (10.5% of the population), 26.9 million with an established diagnosis and 7.3 million undiagnosed people (more than 20%). Mexico is another country with a high rate of diabetics (> 10%) and an increase of 2-3% of more diabetics every 5 years. In Spain, the prevalence of diabetes is close to 8%, with an incidence of 3.7 to 7.9 cases/1000 person-year.

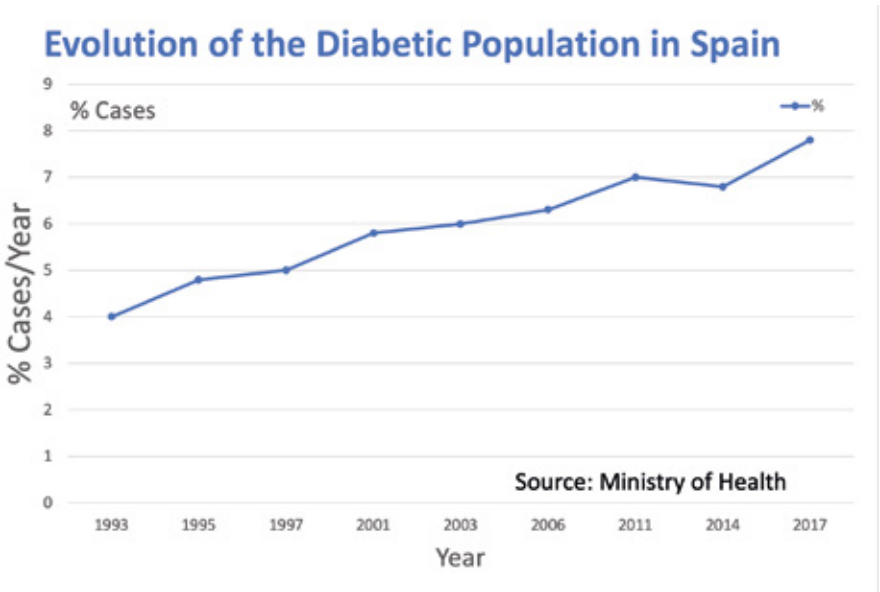
Evolution of diabetes by age group in the United States.



A study by Jean M. Lawrence from the *Department of Research & Evaluation, Kaiser Permanente Southern California*, Pasadena, published in JAMA on August 24, presents alarming figures for the increase in diabetes in children. Among young people aged 19 and under, 4,958 of 3.35 million had type 1 diabetes in 2001, 6,672 of 3.46 million in 2009, and 7,759 of 3.61 million in 2017; Among people ages 10 to 19, 588 out of 1.73 million had type 2 diabetes in 2001, 814 out of 1.85 million in 2009, and 1230 out of 1.85 million in 2017. The estimated prevalence of type 1 diabetes per 1,000 youth aged 19 years and younger increased significantly from 1.48 in 2001 to 1.93 in 2009, to 2.15 in 2017, with an absolute increase of 0.67 per 1,000 youth and a relative increase of 45.1% over 16 years. The largest absolute increases were seen among non-Hispanic whites (0.93 per 1,000 youth) and non-Hispanic blacks (0.89 per 1,000 youth). The estimated prevalence of type 2 diabetes per 1,000 youth aged 10-19 years increased significantly from 0.34 in 2001 to 0.46 in 2009 and to 0.67 in 2017, with an absolute increase of 0.32 per 1,000 youth and a relative increase of 95.3% over 16 years. The largest absolute increases were seen among non-Hispanic blacks (0.85 per 1,000 youth) and Hispanics (0.57 per 1,000 youth).

In a June 25 study, Li Wang and colleagues from China and the US studied diabetes in 28,143 North American adults and observed an increase in diabetes from 9.8% in 1999-2000 to 14.3% in 2017-2018.

Diabetes, like obesity, is strongly influenced by environmental factors associated with diet and physical exercise; but it requires a genomic background to develop in the most vulnerable population. Any program aimed at preventing diabetes must include a genomic risk study; and therapeutic programs to control the levels of sugar and glycated hemoglobin in the affected population must be carried out in a personalized way, using pharmacogenetic protocols, to optimize results and reduce side effects.



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Criteria for diagnosis and treatment of migraine

Migraine is a primary disabling headache that affects more than 1 billion people worldwide. Despite its widespread prevalence, migraine remains underdiagnosed and poorly treated. A panel of experts, led by Anna K. Eigenbrodt from the University of Copenhagen, Denmark, has established a ten-step protocol for the proper management of migraine (see Scheme). These criteria have been reviewed and expanded by the medical team of the International Center of Neurosciences and Genomic Medicine EuroEspes.

Step 1: When to suspect a migraine?
In the third edition of the International Classification of Headache Disorders (ICHD-3), migraine is classified into three main types: migraine without aura, migraine with aura, and chronic migraine. The clinical characteristics of each type must be considered to ensure an accurate diagnosis.
Migraine without aura is suspected in a person with moderate to severe recurrent headache, particularly if the pain is unilateral and/or throbbing, and when the person has accompanying symptoms such as photophobia, phonophobia, nausea, and/or vomiting. Migraine with aura shows the above symptoms and recurrent visual and/or hemisensory disturbances of short duration. Chronic migraine presents with ≥15 headache days per month. The suspicion of migraine is reinforced by a family history of headache and if the onset of symptoms appears around puberty.

Step 2: Diagnosis of migraine
A good migraine diagnosis requires a careful medical history, applying the ICHD-3 criteria and validated diagnostic aids and screening tools, such as headache diaries, the three-item migraine questionnaire, and the five-item migraine screening questionnaire. Before any migraine diagnosis, a thorough differential diagnosis should be made to rule out any other brain problem that may cause a headache. For this, static or functional neuroimaging can be used and in the case of familial vascular risk, molecular diagnostic procedures should also be used.

Step 3. Patient education
Each patient should be given a full explanation of migraine as a disease and the principles of its management. Predisposing and triggering factors should be considered, keeping in mind that the true triggers are often obvious. The patient must adhere to the principles of stepped care to achieve optimal individualized therapy.

Step 4. Acute treatment
Acute treatments can be classified as first-line, second-line, third-line, and adjunct therapy, and should be used with a tiered approach of care. The doctor should offer acute treatment to all people who experience migraine attacks; advise the use of acute treatments at the beginning of the headache attack phase, since efficacy depends on timely use with the correct dose; advise patients that frequent, repeated use of acute medication risks the development of adverse effects and may cause overdose headache. In those cases where the pharmacogenetic profile of the patient allows, non-steroidal anti-inflammatory drugs (NSAIDs) (acetylsalicylic acid, ibuprofen or potassium diclofenac) can be used as first-line drugs. Triptans are second-line medications. Combining triptans with fast-acting NSAIDs may be considered to prevent recurrent relapse. Ditans and gepants are third-line drugs. If necessary, prokinetic antiemetics (domperidone or metoclopramide) can be used as oral adjuncts for nausea and / or vomiting, taking into account that these drugs are antidopaminergics with potential parkinsonian effect in vulnerable people. Oral ergot alkaloids, opiates, and barbiturates should be avoided, except in special circumstances or in patients whose pharmacogenetics do not allow the use of NSAIDs and triptans.

Step 5. Preventive treatment
In patients whose persistent migraine impairs their quality of life despite optimized acute therapy, additional preventive therapy should be considered. In practice, patients who are considered for preventive treatment remain negatively affected for at least 2 days per month, although this should not be considered an absolute rule. Aside from the frequency of the migraine, doctors should always consider factors such as the severity of the attacks, the duration of the attacks (for example, menstruation-related attacks tend to last longer), and migraine-related disability. Another indication for preventive therapy is the excessive use of acute medications.

The implementation of preventive treatment should be considered in patients who are adversely affected by migraine ≥2 days per month despite acute treatment. In these cases, beta-blockers (atenolol, bisoprolol, metoprolol, or propranolol), topiramate, or candesartan can be used as first-line drugs; flunarizine, amitriptyline, or (in men) sodium valproate as second-line medications; CGRP monoclonal antibodies as third-line drugs; and neuromodulatory devices, biobehavioral therapy, and acupuncture as adjuncts to acute and preventive medication or as stand-alone preventive treatment when medication is contraindicated.

Step 6. Management of migraine in special populations (the elderly, children, adolescents, menstruating, pregnant, lactating, and menopausal women).
Migraine often subsides in old age, while the incidence of many secondary headaches increases with age. The onset of a migraine after age 50 should raise suspicion of an underlying cause. In patients with late-onset migraine, the primary cause should be sought. In the elderly, the risks of secondary headache, comorbidities and adverse events should be evaluated. In children and adolescents with migraine, bed rest may be sufficient; if not, if the child's pharmacogenetic profile allows, ibuprofen could be used for acute treatment and propranolol, amitriptyline or topiramate for prevention. In pregnant or lactating women, the use of paracetamol for acute treatment is preferable and preventive medication should be avoided whenever possible. In women with menstrual migraine, perimenstrual preventive therapy with long-acting NSAIDs or a triptan should be considered.

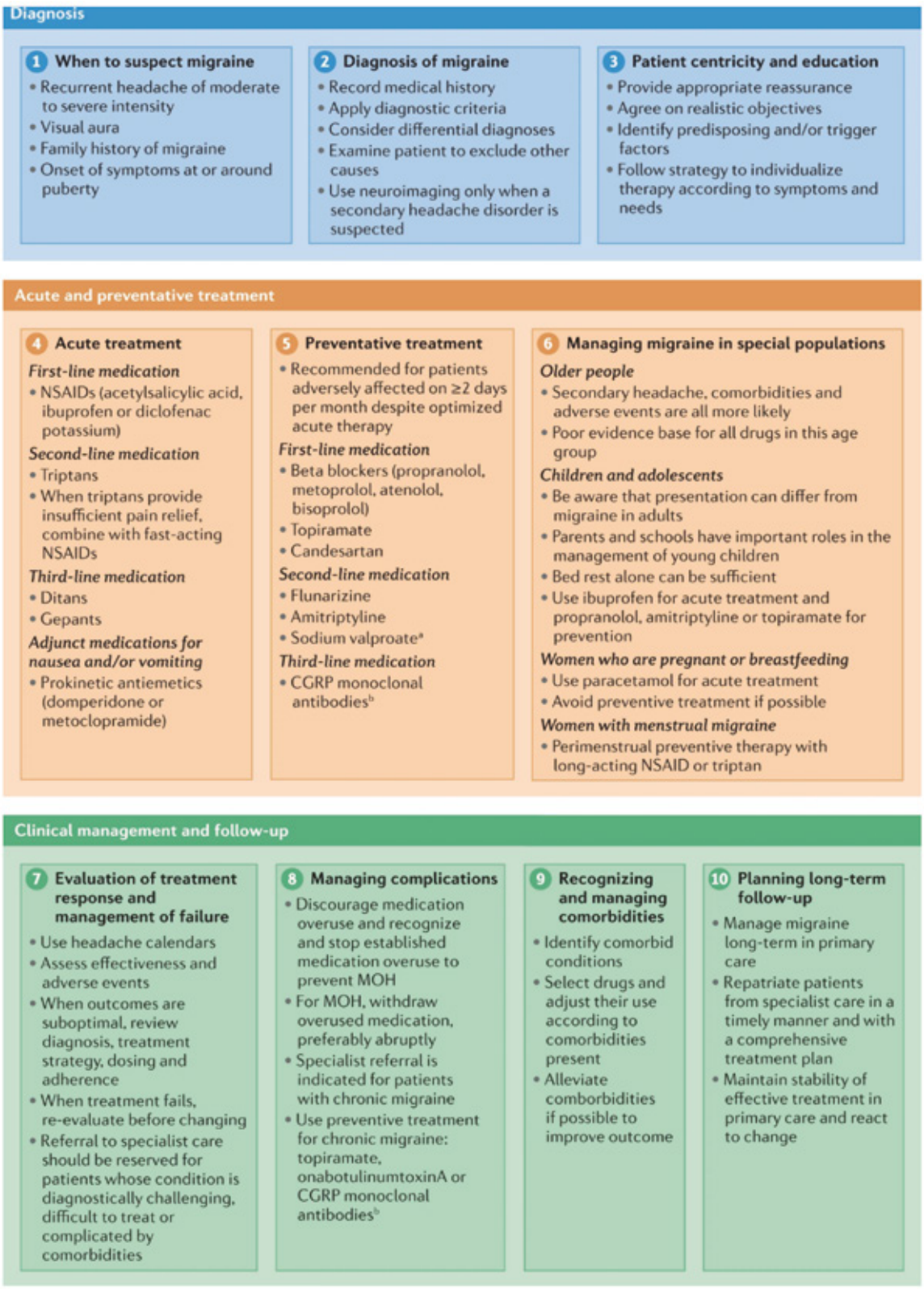
Step 7. Evaluation of treatment response and management of failure
Response to treatment should be assessed within 2-3 months after starting the chosen treatment. Evaluation of responses to treatment should include a review of effectiveness, adverse events, and adherence.

The evaluation of the response to treatment should be quarterly and semi-annually. The effectiveness of the treatment is evaluated by analyzing the frequency of the attack, the severity of the attack and the disability related to the migraine. When results are suboptimal, the diagnosis, treatment strategy, dosage, and adherence should be reviewed. If all treatment fails, the diagnosis is most likely wrong and diagnostic and therapeutic strategies should be rethought.

Step 8. Managing complications
A common complication is migraine due to overdose of analgesics, of which the patient must be aware and avoid falling into this negative practice. In the event of an overdose headache, the doses should be corrected and / or treatment changed. Special care must be taken with opioid overdose. When migraine becomes chronic, other forms of therapeutic intervention should be chosen (topiramate, onabotulinumtoxinA, CGRP monoclonal antibodies).

Step 9. Identification and management of comorbidity
The identification and recognition of concomitant pathologies with migraine is important because they can influence the choice of medication. For example, topiramate is the preferred treatment for obese patients due to its association with weight loss. For patients with depression or sleep disorders, amitriptyline is probably more beneficial. Recognizing comorbidities is also important because alleviating them can improve migraine treatment outcomes, and vice versa.

Step 10. Long-term follow-up
Migraine is a chronic disease that requires long-term treatment and long-term follow-up. Migraine patients should be aware that certain foods and a wide variety of medications can become precipitating or aggravating factors for headaches. Migraine associated with vascular headache is an important risk factor for the development of cerebrovascular accidents in adulthood and old age, and therefore a preventive program is highly recommended.



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Exomic Sequencing of Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) affects 1-2% of the population and, as with other complex neuropsychiatric disorders, various rare mutations are known to contribute to its genetic risk. A study led by Mathew Halvorsen, from the Department of Genetics at the University of North Carolina at Chapel Hill, and a large group of collaborators from other North American universities, demonstrates new genetic mutations associated with OCD. In that study, exome sequencing was performed in the largest OCD cohort in the world, to date, with 1,313 cases (587 triplets, 41 quartets, and 644 singletons of affected individuals). In the case-control (1,263 / 11,580), the most significant result was observed in the *SLITRK5* gene. Across the exome, there was an excess of loss-of-function variation, specifically within genes that are intolerant of loss-of-function. In a trios analysis, an excess of *de novo*-formed damaging variants was found, along with an excess of *de novo* mutations with loss-of-function in intolerant genes.

In addition to these rare variants, OCD shares genetic defects with other neuropsychiatric disorders. Genomic analysis aids the diagnosis of OCD, and the characterization of the pharmacogenetic profile of each patient is essential for the personalization of pharmacological treatment, to optimize the therapeutic effect and to reduce the adverse effects of the psychotropic medication that patients with OCD must consume for years.

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Oxytocin and Alloparental Maternal Behavior

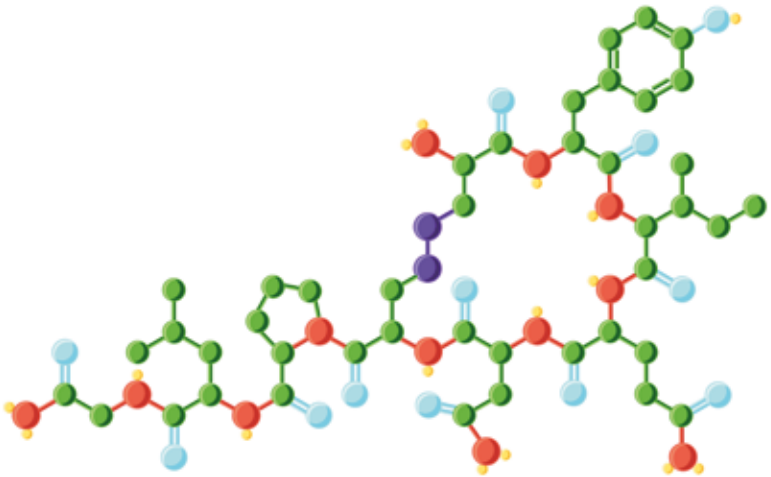
Social interactions, such as bonding and raising children, are fundamental aspects of animal and human behavior. Parental care is especially important and is therefore believed to be at least partially innate or induced after mating. However, maternal behavior can also be acquired from experience. In primates, including humans, non-biological parents can learn to care for children after instruction or observation from experienced caregivers. What is unclear is whether alloparenting (caring for infants by non-parent adults) can be learned from experience in other species, and what neural mechanisms might underlie maternal learning.

The hormone oxytocin is an important molecular signal for maternal behavior. In mammals, oxytocin release from the hypothalamus is associated with parturition and lactation. Oxytocin also works in the brain to increase the prominence of social information and allow alloparenting in mice. Virgin female mice initially ignore hatchlings and ultrasonic distress calls from isolated pups. In contrast, within a few days of co-housing with experienced mothers in litters, most virgin females begin to express alloparental behaviors, including retrieving cubs in the nest. Oxytocin accelerates the onset of puppy recovery, promoting plasticity in the auditory cortex to recognize puppy calls.

In a paper published Aug. 11 in *Nature*, Ioana Carcea and her colleagues at New York University studied the role of oxytocin in learning murine maternal behavior in virgin females co-housed in litters with an experienced mother. The researchers recorded

neuronal activity in the paraventricular nucleus of the hypothalamus where oxytocin is manufactured, which is then transported to the neurohypophysis, for subsequent release into the bloodstream.

Oxytocinergic paraventricular neurons were activated when virgins were enlisted in maternal care by experienced mothers, who herded the virgins in the nest and taught them to care for the cubs. Visual observation by virgins of the behavior of natural mothers produced an activation of oxytocin-producing neurons, which promoted alloparental behavior. Thus, rodents can acquire maternal behavior by social transmission, providing a mechanism to adapt the brains of adult caregivers to infant needs through endogenous oxytocin.



Oxytocin

$C_{43}H_{60}N_{12}O_{12}S_2$

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Covid-19 News

Animal Origin of SARS-CoV-2

In an elegant study published in Science on August 27, Spyros Lytras, Joseph Hughes, and David Robertson from Glasgow, UK, and their colleagues Wei Xia and Xiaowei Jiang of Guangzhou, China, analyze the animal origin of SARS-CoV-2.

Although it was first detected in December 2019, it was inferred that COVID-19 was present in Hubei province, China, for about a month earlier. To understand the origin of the COVID-19 pandemic, it is necessary to go back to 2002. At that time, a new respiratory coronavirus appeared in Foshan, Guangdong province, China, and spread to 29 countries. In all, 8,000 people were infected with the severe acute respiratory syndrome coronavirus (SARS-CoV) before public health measures controlled its spread in 2003. The zoonotic origin of SARS-CoV was later linked to commercially available live animals. Other sporadic events of spread of SARS-CoV from animals took place in Guangzhou, Guangdong, and some researchers working with cultured viruses were infected in laboratory accidents, but eventually SARS-CoV was eliminated from the human population. The trade in susceptible host animals is a major issue in the emergence of SARS and COVID-19.

Three years after the SARS epidemic began, investigations revealed that horseshoe bats (Rhinolophus) in China were harboring coronavirus of the SARS species (SARSr-CoV), which comprises the subgenus Sarbecovirus of the genus Betacoronavirus. It was inferred that a sarbecovirus circulating in horseshoe bats seduced the parent of SARS-CoV in an intermediate animal host, most likely civet cats. Although other potential intermediate hosts for SARS-CoV, in particular raccoon dogs and badgers, were identified, it was a population of civet cats from Chinese markets that appears to have acted as a vehicle for transmission to humans from the horseshoe bat reservoir in the United States. Presumably, a captive civet cat was initially infected by direct contact with bats. Following the SARS epidemic, increased surveillance revealed the immediate threat posed by sarbecoviruses in horseshoe bats. Despite this clear warning, another member of the SARSr-CoV species, SARS-CoV-2, emerged in 2019 and spread with unprecedented efficiency among humans. It has been speculated that the Wuhan Institute of Virology (WIV) in Hubei was the source of the pandemic because no intermediate hosts for SARS-CoV-2 have been identified to date and also because of the geographic location of the WIV.

SARS-CoV-2 first emerged in the city of Wuhan, which is about 1,500 km from the closest natural sarbecovirus identified in bats in Yunnan province. Since their emergence, coronaviruses genetically close to SARS-CoV-2 have been circulating in horseshoe bats, which spread from east to west in China, and in Southeast Asia and Japan. The evolutionarily closest bat sarbecoviruses are estimated to share a common ancestor with SARS-CoV-2 for at least 40 years, demonstrating that these Yunnan-collected viruses are highly divergent from the SARS-CoV-2 progenitor. The first of these viruses identified in Wuhan, RaTG13, is too divergent to be the progenitor of SARS-CoV-2, providing key genetic evidence that undermines the notion of a "lab leak." Three other sarbecoviruses collected in Yunnan (RmYN02, RpYN06, and PrC31) independent of Wuhan, are now the closest bat coronaviruses to SARS-CoV-2.

Sarbecoviruses closely related to the SARS-CoV-2 coronaviruses, which are evolutionarily closer to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been sampled in China, Cambodia, Japan, and Thailand. The phylogenetic tree, inferred from a genomic region, shows sarbecoviruses are closely related to SARS-CoV-2.

Although contagion of the virus may have occurred through direct contact from horseshoe bat to human, the first detected cases of SARS-CoV-2 in December 2019 are associated with

the wet markets of Wuhan. This is consistent with multiple propagation events associated with the animal market in November and December. It is not possible to be sure of the animal source of SARS-CoV-2, but it is true that live animals (civet cats, foxes, mink, raccoon dogs), susceptible to sarbecoviruses, were for sale in the Wuhan markets, including the Huanan Market (identified as the epicenter of the outbreak in Wuhan) throughout 2019. Many of these animals are bred to market their fur and some of these cultivated species - American mink, red foxes, and raccoon dogs - were sold alive for food by Wuhan animal vendors. This suggests a central role for living intermediate host animals, susceptible to SARSr-CoV, as the primary source of the SARS-CoV-2 progenitor to which humans were exposed.

One particular ecological event in China, which disrupted the meat trade and contributed to increased contacts between wildlife and humans, was the shortage of pork products in 2019. This was a direct consequence of the African swine fever virus (ASFV) pandemic, which led to ≈150 million pigs being slaughtered in China, resulting in a reduction in pork supply of ≈11.5 million metric tons in 2019. Although the production of other meat, such as poultry, beef and fish products, increased moderately and China imported more of these products from international markets to mitigate the shortfall, this supply only covered a fraction of the pork losses. associated with ASFV. Consequently, pork prices reached an all-time high in November 2019, with a ≈2.3-fold increase in the wholesale price compared to the previous year. The pork shortage may have led to the consumption of contaminated wild meat.

There are controversial reports of human cases of SARS-CoV-2 in China dating back to contact with imported frozen food and apparently identified SARS-CoV-2 from frozen food, packaging, and storage surfaces. The high demand for pork facilitated the use of cold chain transport for all types of meat, particularly from places with lower prices to those with higher prices, legally (or illegally), which could also include the transport of species susceptible to infection by SARSr-CoV. The World Health Organization (WHO) Report on the Origins of COVID-19 recorded carcasses of wild animals, particularly badgers, left in freezers in the Huanan market, as well as their sale as frozen products in late December 2019.

In general, animal-to-human transmission of SARSr-CoV associated with infected live animals is the most likely cause of the COVID-19 pandemic. However, the massive scale of the cold

chain supply, particularly after the disruption of the meat industry in China caused by slaughter associated with ASFV, suggests that the frozen carcasses of susceptible animals, whether for human or animal consumption, should not be ruled out as contagion agents in the appearance of SARS-CoV-2.

Worryingly, recent experimental evidence shows that pangolin-derived sarbecoviruses (acquired from exposure to horseshoe bats or other infected animals after illegal trafficking in China) can also infect human cells and have spike proteins that are even better at facilitating entry into human cells than SARS-CoV-2. This points to an additional risk of contagion that extends to the more divergent members of the lineage from which SARS-CoV-2 arose and implies frequent effects of contagion from bats to other forms of wildlife.

Humans are now the dominant host species for SARS-CoV-2. The danger is that SARS-CoV-2 could spread from humans to other animal species, which is called reverse zoonosis, as is suspected for white-tailed deer in the United States. Promiscuous infection of several host species by sarbecoviruses means that future effects of SARSr-CoV contagion to wildlife are highly probable, and current vaccines may not be protective against the new variants.

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Vaccine Safety and Effectiveness

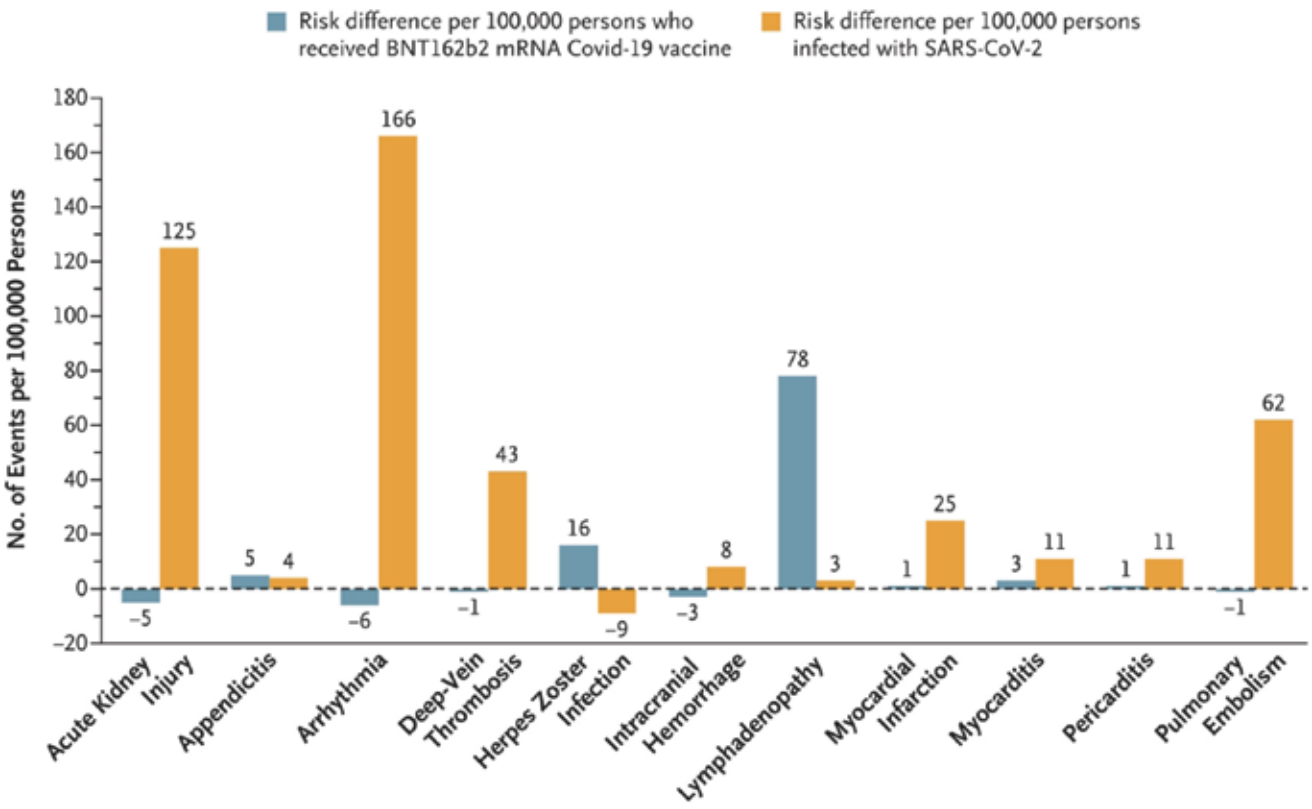
More than 1 year after the 2019 coronavirus pandemic (Covid-19), to prevent severe acute respiratory syndrome (SARS-CoV-2), a mass vaccination effort is underway around the world, with more than 3.4 billion doses administered during the 6-month period since the first vaccines were approved. Pre-approval trials showed that messenger RNA (mRNA)-based vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had a good safety profile; however, these trials were subject to size and patient mix limitations. An evaluation of the safety of the BNT162-2 mRNA vaccine is needed with respect to a wide range of possible adverse events.

This is the work done by Noam Banda and his collaborators, published on August 25 in *The New England Journal of Medicine*. This group used data from Israel's largest health care organization to assess the safety of the BNT162b2 mRNA vaccine, with a similar analysis in SARS-CoV-2 infected individuals and uninfected individuals testing the same adverse events in cases of vaccination and infection by SARS-CoV-2.

In the vaccination analysis, the vaccinated and control groups each included an average of 884,828 people. Vaccination was most strongly associated with an elevated risk of myocarditis (2.7 events per 100,000 people), lymphadenopathy (78.4 events per 100,000 people), appendicitis (5.0 events per 100,000 people), and herpes zoster infection (15.8 events per 100,000 people). SARS-CoV-2 infection was associated with a substantially increased risk of myocarditis (11.0 events per 100,000 people) and additional serious adverse events, including pericarditis, arrhythmia, deep vein thrombosis, pulmonary embolism, myocardial infarction, intracranial hemorrhage, and thrombocytopenia. In this study, in a nationwide mass vaccination setting, the BNT162b2 vaccine was not associated with an elevated risk for most of the adverse events examined. The vaccine was associated with an excess risk of myocarditis (1 to 5 events per 100,000 people). The risk of this potentially serious adverse event and many other serious adverse events increased substantially after SARS-CoV-2 infection.

This type of study demonstrates the safety of the vaccine, but does not guarantee efficacy. A vaccine is given to help the immune system fight the viral infection effectively; however, a high percentage of vaccinated patients (10-15%) are infected and more than 20% do not reach anti-SARS-Cov-2 antibody values above 500 U/mL.

Absolute excess risk of various adverse events after vaccination or SARS-CoV-2 infection.



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Global Vaccination: The debate in Children and Adolescents

As the extraordinarily infectious Delta variant of SARS-CoV-2 continues to spread around the world, the powers of vaccines are showing their limits. Although they remain effective in preventing severe COVID-19, the tantalizing hope that vaccines can block nearly all infections and stifle transmission has evaporated. That has disrupted plans to return to the office and school, threatened economic recovery, and spurred new political disputes over mask and vaccination mandates. While new studies hint that vaccine-induced immunity may be waning, lawmakers and scientists are debating whether generalized booster vaccines could help or whether unvaccinated vaccines should remain the top priority. Many people wonder if a booster will be enough or if regular vaccination against COVID-19 will become the new normality, as it is for influenza.

The FDA has approved the use of the Pfizer-BioNTech vaccine for people 16 years of age and older. This landmark decision, the first full approval of a vaccine for COVID-19, is sure to clear the way for companies, hospitals and government agencies that have not yet done so to adopt vaccine mandates for their employees. For colleges and universities, the FDA's decision may be big news, welcomed by some and repudiated by others.

A topic of scientific and public debate is whether or not to vaccinate children. Some argue that a SARS-CoV-2 vaccine for children and adolescents would play an important role in containing the COVID-19 pandemic. On June 28, the Chinese presented the first study with the CoronaVac vaccine, which contains inactivated SARS-CoV-2, in children and adolescents aged 3 to 17 years. The double-blind, randomized, controlled, phase 1-2 clinical trial was conducted in healthy children and adolescents aged 3 to 17 years at the Hebei Provincial Center for Disease Control and Prevention in Zanhuang (Hebei, China). People with exposure to SARS-CoV-2 or a history of infection were excluded. The vaccine (in 0.5 mL aluminum hydroxide adjuvant) or aluminum hydroxide alone (alum only, control) was administered by intramuscular injection in two doses (day 0 and day 28). A phase 1 trial was performed in 72 participants with an age de-escalation in three groups and a dose escalation in two blocks (1.5 μg or 3.0 μg per injection). Within each block, participants were randomly assigned (3: 1) via block randomization to receive CoronaVac or alum alone. In phase 2, participants were randomized (2:2:1) by block randomization to receive CoronaVac at doses of 1.5 μg or 3.0 μg. The primary immunogenicity endpoint evaluated in the per protocol population was the seroconversion rate of the neutralizing antibody to live SARS-CoV-2 at 28 days after the second injection.

Between October 31, 2020 and December 2, 2020, 72 participants enrolled in phase 1, and between December 12, 2020 and December 30, 2020, 480 participants enrolled in phase 2. 550 participants received at least one dose of vaccine or alum alone. In the combined phase 1 and phase 2 safety profile, any adverse reaction within 28 days after injection occurred in 56 (26%) of 219 participants in the 1.5 μg group, 63 (29%) of 217 in the 3.0 μg group and 27 (24%) of 114 in the control group, without significant differences. The majority of adverse reactions were mild or moderate in severity. Injection site pain was the most frequently reported event (73 [13%] of 550 participants), occurring in 36 (16%) of 219 participants in the 1.5 μg group, 35 (16%) of 217 in the 3.0 μg group and two (2%) in the control group. As of June 12, 2021, only one serious adverse event of pneumonia had been reported in the control group, which was considered unrelated to vaccination. In phase 1, neutralizing antibody seroconversion was observed after the second dose in 27 of 27 participants (100.0%) in the 1.5 μg group and 26 of 26 participants (100.0%) in the 3.0 μg group, with geometric mean titers of 55.0 and 117.4. In phase 2, seroconversion was observed in 180 of 186 participants (96.8%) in the 1.5 μg group and 180 of 180 participants (100.0%) in the 3.0 μg group, with geometric mean titers of 86.4 and 142.2.

Based on these results, the Chinese consider that CoronaVac was well tolerated and safe and induced humoral responses in children and adolescents aged 3 to 17 years. Neutralizing antibody titers induced by the 3.0 µg dose were higher than those of the 1.5 µg dose. The results support the use of 3.0 µg doses in two-dose vaccination programs.

The temptation of large-scale, global vaccination to cover the entire population is considered by many to be unethical and unnecessary (Science 27 Aug 2021: Vol. 373, Issue 6558, pp. 949-950; DOI: 10.1126 / science.373.6558.949).

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Mental Health in times of Pandemic

The public health crisis from the COVID-19 pandemic poses serious threats to people's health. In a survey of 1,210 participants from 194 Chinese cities, 54% reported moderate to severe distress, 29% anxiety, and 17% symptoms of depression. In another survey conducted in Germany during the first lockdown, between March 27 and April 6, 2020, 25% of the participants showed serious symptoms of anxiety and depression. In another German survey of 15,000 people in March 2020, 45% showed generalized anxiety, 15% depression, and 59% pathological fear of COVID-19. In a meta-analysis of 43 studies conducted in Asia and Europe, it was observed that anxiety rates tripled (25%) compared to pre-pandemic studies (7%). Other studies in different populations showed anxiety and depression figures above 30%.

In a study published on July 22 in *Scientific Reports*, Beutel et al verified a notable increase in psychiatric symptoms in the German population, especially related to stress, anxiety, depression and a feeling of loneliness, in the last year.

This phenomenon, common in different parts of the world, should make politicians and communicators think about the need for a change in the communication strategies and handling of pandemic information so as not to increase emotional instability in the population, already punished by the vicissitudes of the pandemic.

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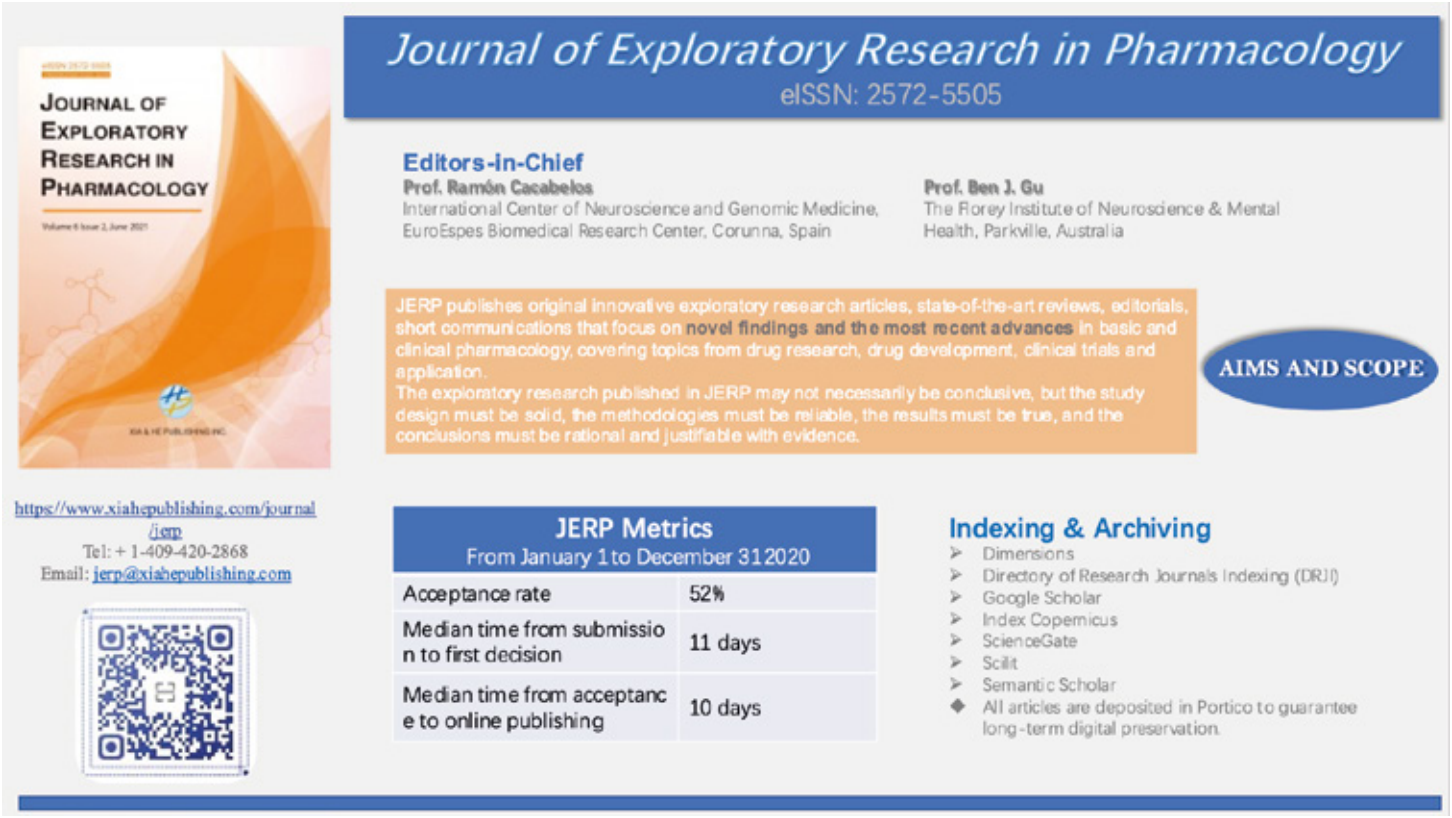
Editorial News

The Xia Publishing company, publisher of the ***Journal of Exploratory Research in Pharmacology*** (JERP), based in China and the USA, has appointed Dr. Ramón Cacabelos Editor-in-Chief of JERP. Dr. Cacabelos was Editor-in-Chief and founder of JERP in 2015, a position he voluntarily resigned three years later; he is now once again taking over the editorial command of this interesting journal that offers opportunities for scientific dissemination to young researchers and well-established scientists in the field of pharmacological innovation.



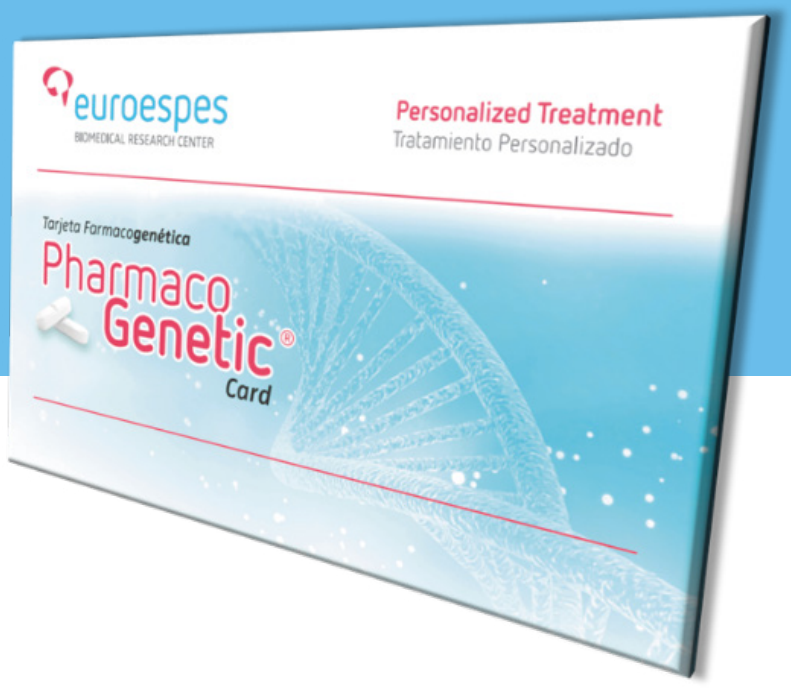
Promotional Section

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

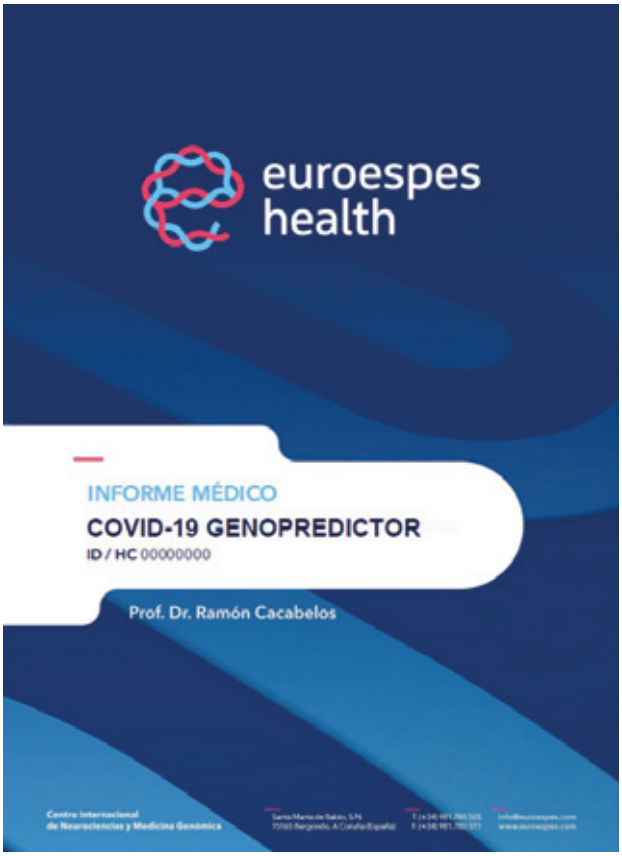
The PPP identifies the population at risk of suffering from Parkinson's disease, differentiating familial Parkinson's disease and other forms of parkinsonism (vascular, toxic or traumatic). The PPP also includes (i) a home PPP for all those asymptomatic people with a family history of Parkinson's or 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.

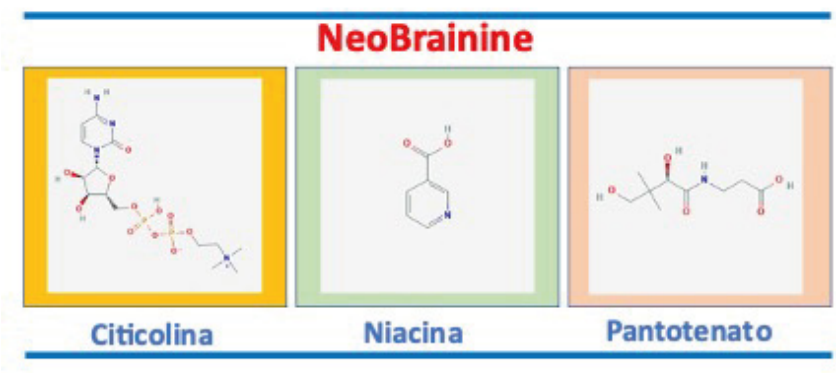
NeoBrainine

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.

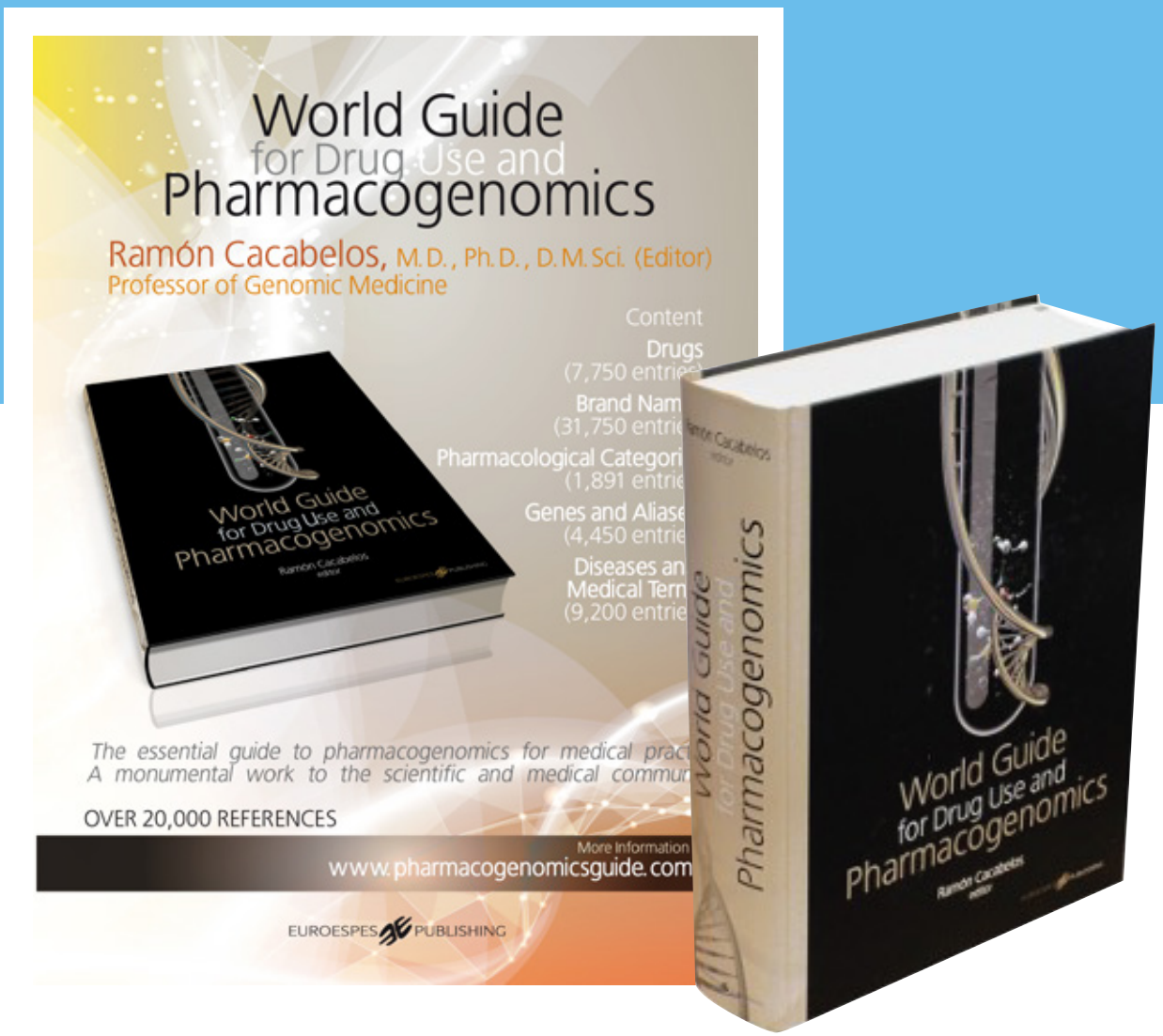
DermoGenetics Catalog

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.

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