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Special article

Precision Medicine: *Precisely* now☆

Medicina de precisión: *precisamente* ahora

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Concepts of Precision Medicine and Personalized Medicine

The term "P4 Medicine" (*preventive*, *predictive*, *personalized* and *participatory*) was coined by Leroy Hood–founder of the Institute for Systems Biology of Seattle – to refer to a form of medicine that would go beyond the mere diagnostic and therapeutic process of diseases and that pursued the maximum welfare in people's health.[1] With the support of technology, this author suggested that the medical history and the current state of health of a patient could be defined through a huge set of virtual data, which could in turn be used for diagnostic, therapeutic and preventive purposes. That huge amount of information from a single individual could be added to that from millions of similar people to build algorithms that would predict future medical needs for the global population and for each individual. Therefore, a fifth P is added to the 4Ps already mentioned, which would refer to extending this objective to the population as a whole *(population)*.[2] The concept of Precision Medicine normally refers to the potential advantages of having information about a person's genome, lifestyle and environment when making decisions about their health, thus, this term would be encompassed in the broader "patient-centred medicine" or "Personalized Medicine" notion.[3] The ultimate goal of Precision Medicine is to provide extensive personalized information thanks to the precise use of integrated, complex scientific information.[4]

A practical example of Precision Medicine and Personalized Medicine

The following patient went to the doctor's surgery: a 59-year-old man who, in general, enjoys good health. Never smoked, moderate alcohol consumption. However, he was concerned about a suboptimal control of his blood pressure (very often above 140/90 mmHg) despite a low salt diet and a combination drug treatment based on angiotensin-converting enzyme inhibitors and thiazides; in addition, he conveys his concerns about his father having had prostate and bladder cancer and his mother–who is still alive–was suffering from osteoarthritis, hypertension and type 2 diabetes. Our patient is obese (his weight is 116 kg for a height of 181 cm) and has tried several diets, with which he has been able to lose some weight, gaining the weight back quickly. His primary care doctor has informed him that he has prediabetes and that, unless he loses weight, "he will become diabetic in a short time". He undergoes a complete blood test once a year and a prostate-specific antigen or PSA determination every 2 years. He recently observed an increase up to 3.8 ng/ml in serum PSA levels, although not exceeding the 4 ng/ml which, according to his doctor, is the value from which "biopsies of the prostate should be considered". On the other hand, our patient has always been reluctant to have a colonoscopy, since he does not have any type of digestive symptomatology.

A conventional medicine approach would prompt us to suggest that the patient follows a healthy lifestyle, a balanced low-salt Mediterranean diet, a moderate caloric restriction and a moderate-intensity physical activity, at least 150 min a week. We would consider the need to introduce a third antihypertensive drug, probably a calcium-antagonist. We would make a theoretical calculation of his cardiovascular risk and decide if the patient's condition is compatible with initiating treatment with statins, based on cholesterol levels. If the patient ended up developing

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diabetes uncontrolled with diet and physical exercise, we would choose to prescribe metformin and would probably avoid prescribing thiazolidinediones due to a family history of bladder cancer. In addition, we would explain the convenience of undergoing a screening colonoscopy every 5 years and the futility, in his particular case, of undergoing low-radiation CT scans for lung cancer screening. Finally, we could probably wait to see the progression of PSA values over time, given that 4 ng/ml had not been exceeded, a value accepted as a general rule to consider prostate cancer screening.

Even in compliance with the standards, under a Precision Medicine approach and without imposed restrictions, we would adjust the guidelines described above with the following tweaks: on the one hand, although the macronutrient composition of a hypocaloric diet does not predict its efficacy for most of the population, recent studies suggest that carriers of the C allele in *FGF21* (chromosome 19 gene regulating the activity of 3-hydroxy-3-methylglutaryl-CoA synthetase 2) have a poor response to a low-carb and proportionally high-fat diet and a better response to a high-carb and low-fat diet, as far as total fat reduction and central obesity decrease is concerned.[5] Thus, a determination of this polymorphism could be considered for a better definition of the proportional composition of macronutrients in his diet.

On the other hand, although in women the presence of the C allele in position rs2106809 of the *ACE2* gene has demonstrated to be a predictor of antihypertensive response in patients treated with ACEI, the same is not true for men.[6] However, knowing that the patient is homozygous for *MTHFR* (677TT) and supplementing the treatment with riboflavin, results in a blood pressure reduction of between 6 and 13 mmHg, regardless of the antihypertensive treatment.[7] In that case, one could try to maintain the same antihypertensive regimen, in addition to diet and physical exercise, until the response to the addition of riboflavin can be assessed. The patient has risk factors for developing type 2 diabetes mellitus; however, knowing the genetic variation common in the known polymorphisms would not provide relevant information on the conventional predictive clinical factors in this regard. Nevertheless, we could have optimized their classification into risk groups to predict the development of diabetes if they had been under 50 years of age.[8]

Finally, although as a general rule, a prostate biopsy is not usually performed in adenocarcinoma screening until PSA values are above 4 ng/ml, we could adopt a different approach if we had information about the presence of risk alleles for the following genes: *TERT* (chromosome 5; rs2736098: risk allele, A); *FGFR2* (chromosome 10; rs10788160 risk allele, A); *TBX3* (chromosome 12; rs11067228; risk allele, A); and *KLK3* (chromosome 19; rs17632542; risk allele, T). The agglutination of several of the risk alleles could determine different approaches for similar values of PSA.[9]

Personalized Medicine would go one step further: in addition to taking advantage of genetic information and applying the standards of evidence-based medicine, we can establish a personalized health plan for each patient that also takes into account social, cultural, economic, occupational and other types of variables. Empathy with the patient is essential in Personalized Medicine: try to understand why the patient's environment does not favour a long-term low-salt, balanced diet with a moderate caloric restriction; analyze the customs and leisure habits of the patient and his/her working conditions in order to suggest a realistic physical exercise plan; identify behavioural patterns similar to those of the index patient in the rest of the family and work environment, which could benefit from a simple early intervention; and empower the patient so that he or she has sufficient training to ensure compliance with the objectives and an adequate autonomous decision making process, guided by a multidisciplinary team of professionals.

Additional implications of Precision Medicine

As we have seen, knowledge of the patient's genetic information can determine a different management of his/her pathology, which, for the case described, have to do with prevalent diseases that are inherited following a complex inheritance pattern, in contrast to genetic-based diseases that are inherited through a monogenic pattern. The key utilities of Precision Medicine are diagnostic, preventive and therapeutic.[10] The presence of certain genetic variants could determine avoiding certain drugs or modifying their dose. Genomic information would have applications in the screening of processes or in the prioritization of some treatments over others. However, for the information to be useful, it must have analytical (accurate and reliable tests) and clinical (related to the disease or the outcome of interest) *validity*, clinical applicability or *utility* (the information has a favourable impact on the clinical progression of the patient), and finally it should not create conflicts due to its possible ethical, legal and social implications.[11,12]

Therefore, Precision Medicine, defends the idea that the "standard patient" does not exist: there is a wide range of treatment effects on patients, almost as many as patients. However, trying to personalize all medical treatments and devices to an individual scale may be too ambitious. In this regard, the *National Research Council* Committee of the USA specifies that Precision Medicine should focus on the classification of people in subpopulations that differ and can, therefore, be grouped in their susceptibility to suffer a disease, biology or prognosis of those morbid processes that could develop, or in their response to specific treatments, so that preventive or therapeutic interventions can be concentrated on the subjects that could benefit from them, thus saving on costs and avoiding side effects in the rest of patients.[13]

Most currently available drugs have been evaluated in trials that classify patients into symptom-based disease groups, instead of classifying them into better defined categories according to biological processes, under the theoretical assumption that symptom-based grouping confers homogeneity to the group and that the subjects will have similar responses to the treatments. In contrast, large databases derived from genetic sequencing over very large populations are currently being used to systematically re-evaluate previous claims about the pathogenicity of different genetic variants.[14] Taking these concepts to the extreme, there have even been attempts to reclassify diseases through biomarkers.[15] Also, in this sense, new biological parameters are generating interest: for example, the microbiome or ecological community of commensal and pathogenic microorganisms of our skin and mucous membranes attracts more and more the attention of a part of the scientific community thanks to advances in DNA sequencing and their diagnostic and therapeutic potentials.[16]

Limitations of Precision Medicine

The first limitations are imposed by the concepts of analytical and clinical validity and of real utility in medical practice. Analytical validity may be more important than previously thought: in an experimental study for which the complete genome of 12 healthy volunteers was genotyped, it was concluded that up to 19% of the genes responsible for known hereditary diseases were not properly sequenced in samples for the discovery of single nucleotide variants; in addition, the genotyping concordance was only moderate (53–59%) for insertion/deletion type genetic variations, which implies a low reproducibility in the detection of genetic variation with a greater potential impact on the origin of certain diseases; finally, in this study there were interobserver discrepancies regarding the need for a clinical follow-up derived from the finding of potential disease-causing variants.[17] This last conflict is not